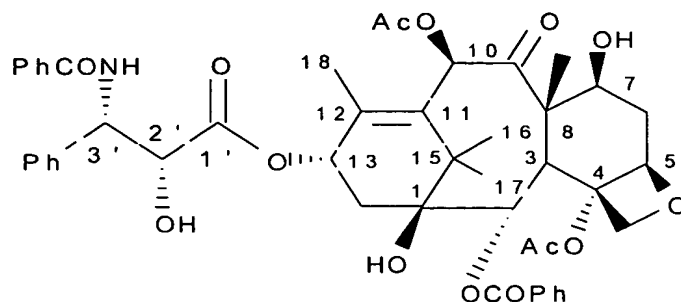# 14-HYDRIDO-9β-HYDROXYTETRACYCLIC TAXANES

REFERENCE TO RELATED APPLICATIONS

This application is a continuation application based on U.S. Serial No. 10/208,418, filed July 30, 2002 which is a continuation of Serial No. 09/566,970, filed May 9, 2000, now U.S. Patent 6,495,704, which is a continuation of Serial No. 08/522,307, filed October 30, 1995, now U.S. Patent 6,066,747, which is a 371 of PCT/US94/02382, filed March 4, 1994, which is a continuation-in-part of Serial No. 08/026,978, filed March 5, 1993, now U.S. Patent 5,990,325 and a continuation-in-part of Serial No. 08/095,087, filed July 20, 1993, now abandoned.
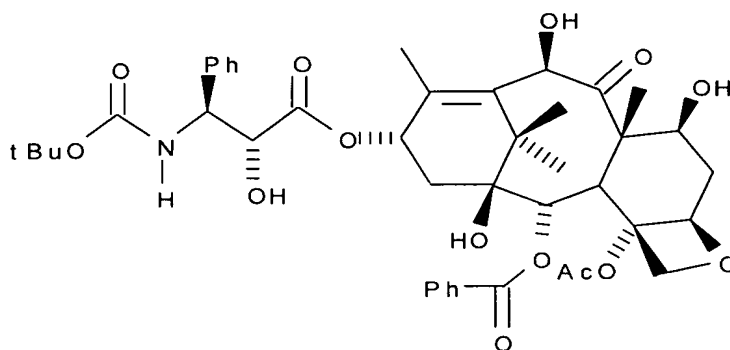
BACKGROUND OF THE INVENTION

The present invention relates to a process for the preparation of taxol, baccatin III and 10-desacetyl-baccatin III derivatives or other taxanes having new C9 functional groups.

Taxol is a natural product extracted from the bark of yew trees. It has been shown to have excellent antitumor activity in in vivo animal models, and recent studies have elucidated its unique mode of action, which involves abnormal polymerization of tubulin and disruption of mitosis. It is currently undergoing clinical trials against ovarian, breast and other types of cancer in the United States and France and preliminary results have confirmed it as a most promising chemo-therapeutic agent. The structure of taxol and the numbering system conventionally used is shown below; this numbering system is also applicable to compounds used in the process of the present invention.

In Colin U.S. Patent No. 4,814,470, it was reported
that a taxol derivative, commonly referred to as taxotere,
has an activity significantly greater than taxol. Taxotere
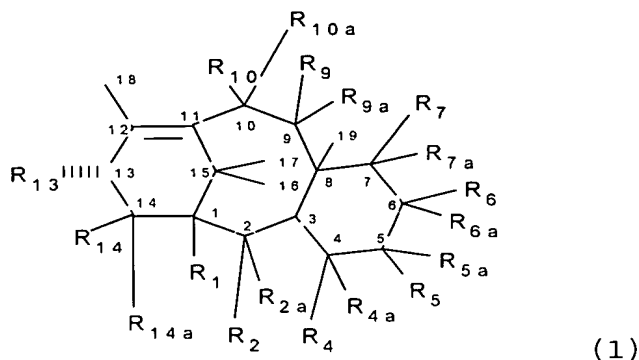has the following structure:

The tetracyclic core of taxol and taxotere bear a C9
keto substituent which, if modified, would lead to the
preparation of a series of taxol analogs having improved
water solubility. To date, however, the selective
manipulation of the C9 keto group has presented a
formidable problem.

SUMMARY OF THE INVENTION

Among the objects of the present invention, therefore,
is the provision of a process for selectively manipulating
the C9 keto substituent of baccatin III, 10-deactylbaccatin
III and other taxanes; and the provision of such a process
which is relatively straightforward.

Briefly, therefore, the present invention is directed
to a process for the preparation of analogs or derivatives
of taxol, baccatin III, 10-desacetyl baccatin III or other

taxanes in which the C9 keto substituent is reduced to the corresponding hydroxy group. Optionally, the C9 hydroxy substituent may thereafter be selectively replaced by another functional group and/or other substituents of the taxane may be replaced by other functional groups to yield a taxane having the formula:

$$R_{10a}$$

(1)

wherein

R$_1$ is hydrogen, hydroxy, protected hydroxy or together with R$_{14}$ forms a carbonate;

R$_2$ is hydrogen, hydroxy, -OCOR$_{31}$, or together with R$_{2a}$ forms an oxo;

R$_{2a}$ is hydrogen or together with R$_2$ forms an oxo;

R$_4$ is hydrogen, together with R$_{4a}$ forms an oxo, oxirane or methylene, or together with R$_{5a}$ and the carbon atoms to which they are attached form an oxetane ring;

R$_{4a}$ is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cyano, hydroxy, -OCOR$_{30}$, or together with R$_4$ forms an oxo, oxirane or methylene;
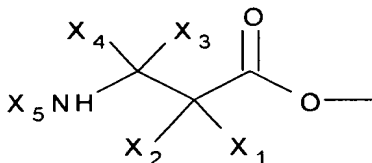
R$_5$ is hydrogen or together with R$_{5a}$ forms an oxo;

R$_{5a}$ is hydrogen, hydroxy, protected hydroxy, acyloxy, together with R$_5$ forms an oxo, or together with R$_4$ and the carbon atoms to which they are attached form an oxetane ring;

R$_6$ is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl, hydroxy, protected hydroxy or together with R$_{6a}$ forms an oxo;

R$_{6a}$ is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl, hydroxy, protected hydroxy or together with R$_6$ forms an oxo;

3

R_7 is hydrogen or together with R_{7a} forms an oxo;

R_{7a} is hydrogen, halogen, protected hydroxy, $-OR_{28}$, or together with R_7 forms an oxo;

R_9 is hydrogen;

R_{9a} is hydrogen, hydroxy, protected hydroxy, or acyloxy;

R_{10} is hydrogen or together with R_{10a} forms an oxo;

R_{10a} is hydrogen, $-OCOR_{29}$, hydroxy or protected hydroxy, or together with R_{10} forms an oxo;
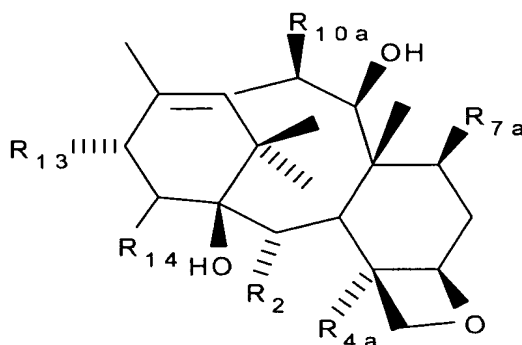
R_{13} is hydroxy, protected hydroxy or

R_{14} is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl, hydroxy, protected hydroxy or together with R_1 forms a carbonate;

R_{14a} is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

R_{28} is hydrogen, acyl, or hydroxy protecting group;

R_{29}, R_{30} and R_{31} are independently hydrogen, alkyl, alkenyl, alkynyl, monocyclic aryl or monocyclic heteroaryl;

X_1 is $-OX_6$, $-SX_7$, or $-NX_8X_9$;

X_2 is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_3 and X_4 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

X_5 is $-COX_{10}$, $-COOX_{10}$, $-COSX_{10}$, $-CONX_8X_{10}$, or $-SO_2X_{11}$;

X_6 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or hydroxy protecting group;

X_7 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or sulfhydryl protecting group;

X_8 is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterosubstituted alkyl, alkenyl, alkynyl, aryl or heteroaryl;

X_9 is an amino protecting group;

X_{10} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterosubstituted alkyl, alkenyl alkynyl, aryl or heteroaryl;

X_{11} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-OX_{10}$, or $-NX_8X_{14}$; and

X_{14} is hydrogen, alkyl, alkenyl, alkynyl, aryl, or heteroaryl.

The present invention is additionally directed to a derivative of baccatin III or 10-desacetyl baccatin III having the following formula which is a key inter-mediate in the synthesis of a new series of tetracyclic taxanes

wherein R_2, R_{4a}, R_{7a}, R_{10a} and R_{14} are as previously defined and R_{13} is hydroxy or protected hydroxy.

Other objects and features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE INVENTION

As used herein "Ar" means aryl; "Ph" means phenyl; "Ac" means acetyl; "Et" means ethyl; "R" means alkyl unless otherwise defined; "tBu" means t-butyl; "TES" means triethylsilyl; "TMS" means trimethylsilyl; "TPAP" means tetrapropylammonium perruthenate; "DMAP" means p-dimethylamino pyridine; "DMF" means dimethyl-formamide; "LDA" means lithium diisopropylamide; "LAH" means lithium aluminum hydride; "Red-Al" means sodium bis(2-methoxyethoxy) aluminum hydride; "10-DAB" means 10-desacetylbaccatin III; protected hydroxy means -OR wherein R is a hydroxy protecting group; sulfhydryl protecting group" includes, but is not limited to, hemithioacetals

such as 1-ethoxyethyl and methoxymethyl, thioesters, or
thiocarbonates; "amine protecting group" includes, but is
not limited to, carbamates, for example,
2,2,2-trichloroethylcarbamate or tertbutylcarbamate; and
"hydroxy protecting group" includes, but is not limited to,
ethers such as methyl, t-butyl, benzyl, p-methoxy-benzyl,
p-nitrobenzyl, allyl, trityl, methoxymethyl,
methoxyethoxymethyl, ethoxyethyl, tetrahydropyranyl,
tetrahydrothiopyranyl, and trialkylsilyl ethers such as
trimethylsilyl ether, triethylsilyl ether, dimethylaryl-
silyl ether, triisopropylsilyl ether and t-butyldimethyl-
silyl ether; esters such as benzoyl, acetyl, phenyl-acetyl,
formyl, mono-, di-, and trihaloacetyl such as chloroacetyl,
dichloroacetyl, trichloroacetyl, trifluoro-acetyl; and
carbonates including but not limited to alkyl carbonates
having from one to six carbon atoms such as methyl, ethyl,
n-propyl, isopropyl, n-butyl, t-butyl; isobutyl, and
n-pentyl; alkyl carbonates having from one to six carbon
atoms and substituted with one or more halogen atoms such
as 2,2,2-trichloroethoxymethyl and 2,2,2-trichloroethyl;
alkenyl carbonates having from two to six carbon atoms such
as vinyl and allyl; cycloalkyl carbonates have from three
to six carbon atoms such as cyclopropyl, cyclobutyl,
cyclopentyl and cyclohexyl; and phenyl or benzyl carbonates
optionally substituted on the ring with one or more C_{1-6}
alkoxy, or nitro. Other hydroxyl, sulfhydryl and amine
protecting groups may be found in "Protective Groups in
Organic Synthesis" by T. W. Greene, John Wiley and Sons,
1981.

The alkyl groups described herein, either alone or
with the various substituents defined hereinabove are
preferably lower alkyl containing from one to six carbon
atoms in the principal chain and up to 15 carbon atoms.
They may be straight or branched chain and include methyl,
ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl,
aryl, hexyl, and the like.

The alkenyl groups described herein, either alone or with the various substituents defined herein-above are preferably lower alkenyl containing from two to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include ethenyl, propenyl, isopropenyl, butenyl, iso-butenyl, aryl, hexenyl, and the like.

The alkynyl groups described herein, either alone or with the various substituents defined herein-above are preferably lower alkynyl containing from two to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, aryl, hexynyl, and the like.

The aryl moieties described herein, either alone or with various substituents, contain from 6 to 15 carbon atoms and include phenyl. Substituents include alkanoxy, protected hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino, amido, etc. Phenyl is the more preferred aryl.

The heteroaryl moieties described herein, either alone or with various substituents, contain from 5 to 15 atoms and include, furyl, thienyl, pyridyl and the like. Substituents include alkanoxy, protected hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino, amido, etc.

The acyloxy groups described herein contain alkyl, alkenyl, alkynyl, aryl or heteroaryl groups.
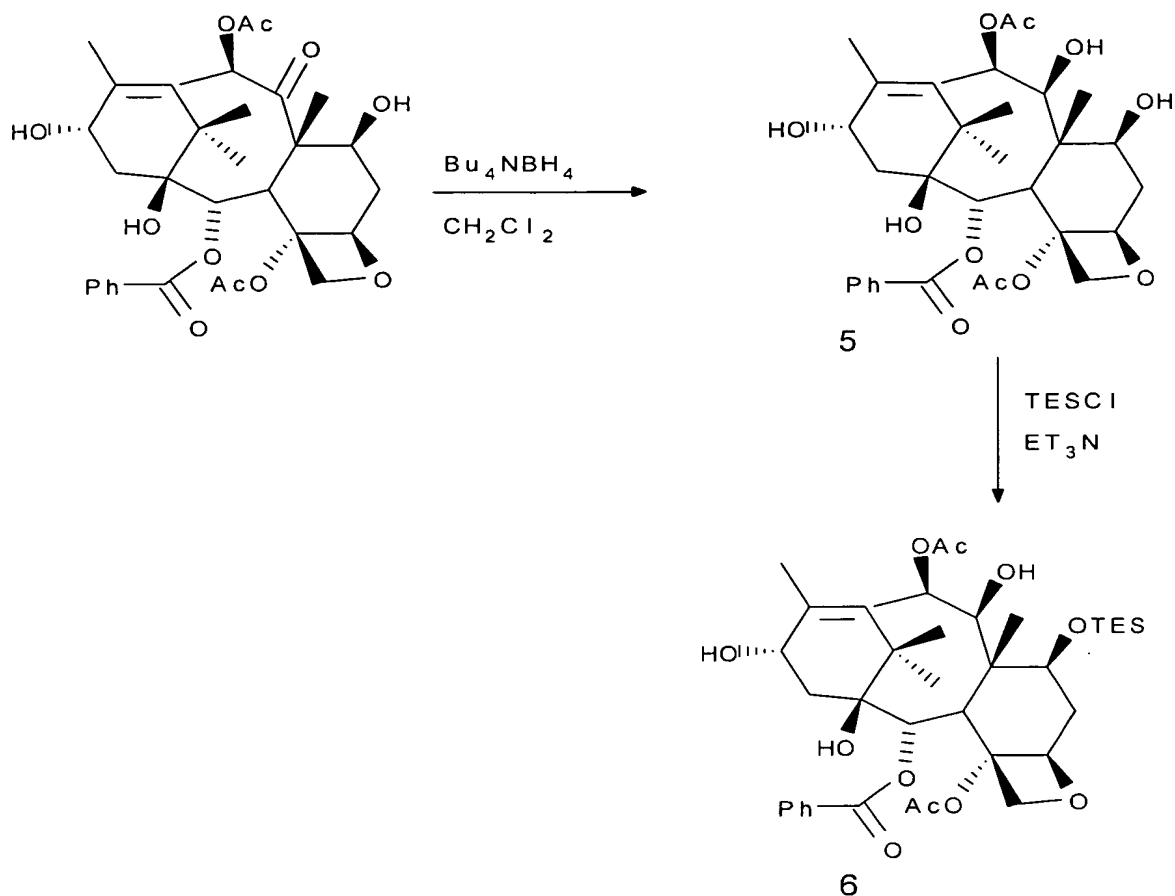
The substituents of the substituted alkyl, alkenyl, alkynyl, aryl, and heteroaryl groups and moieties described herein, may be alkyl, alkenyl, alkynyl, aryl, heteroaryl and/or may contain nitrogen, oxygen, sulfur, halogens and include, for example, lower alkoxy such as methoxy, ethoxy, butoxy, halogen such as chloro or fluoro, nitro, amino, and keto.

In accordance with the present invention, it has been discovered that the C9 keto substituent of a taxane having a C9 keto and a C7 hydroxy substuent may be selectively

reduced to yield the corresponding C9 β-hydroxy derivative. The reducing agent is preferably a an aluminum hydride or a borohydride such as triacetoxyborohydride, more preferably a tetraalkylborohydride or tetraalkylaluminumhydride, and most preferably, tetra-butylammoniumborohydride (Bu_4NBH_4).
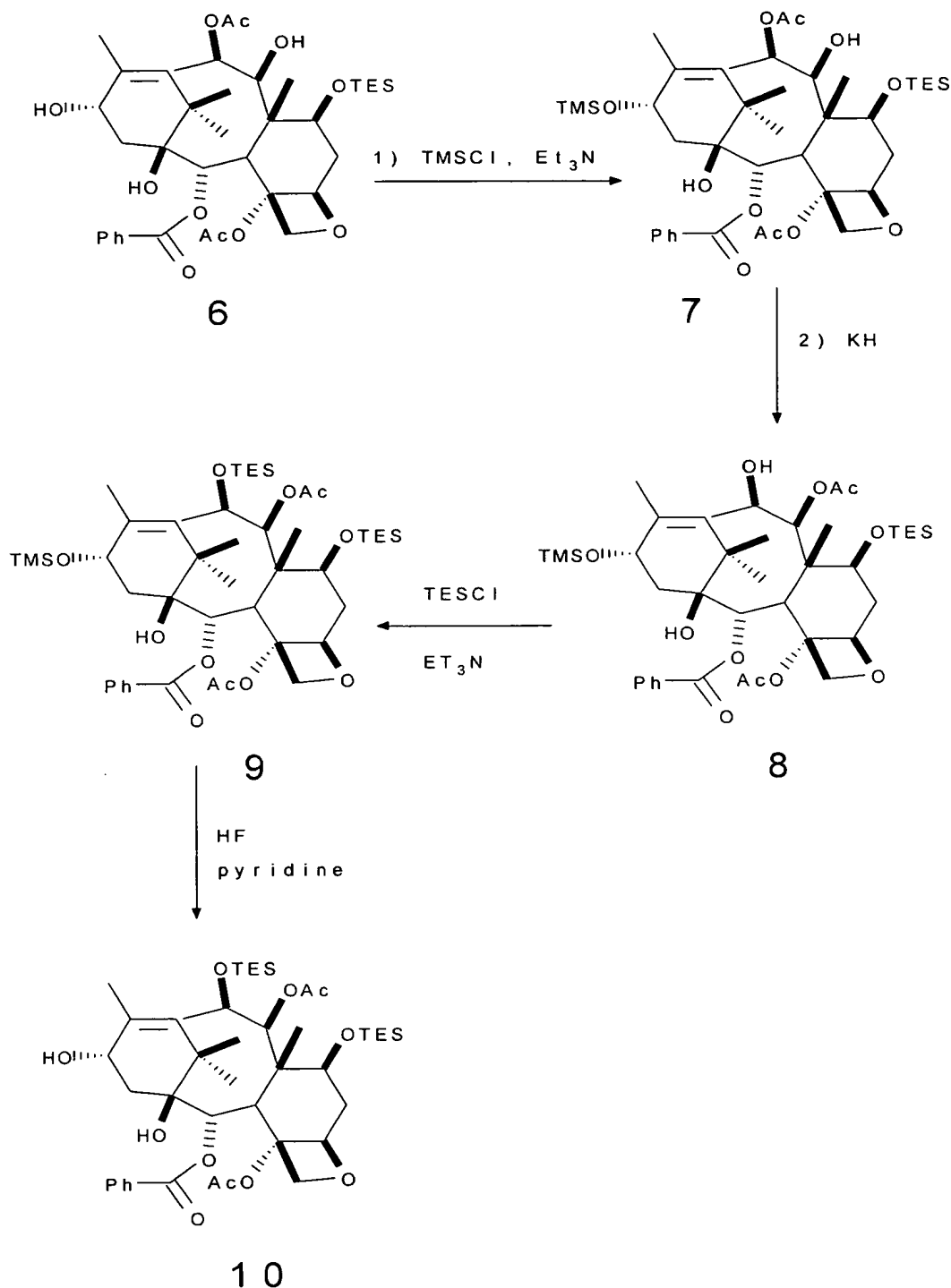
As illustrated in Reaction Scheme 1, the reaction of baccatin III with Bu_4NBH_4 in methylene chloride yields 9-desoxo-9β-hydroxybaccatin III **5**. After the C7 hydroxy group is protected with, for example, the triethylsilyl protecting group, a suitable side chain may be attached to 7-protected-9ß-hydroxy derivative **6** as set forth in U.S. Patent Nos. 4,924,011 and 4,924,012 or by reaction with a β-lactam as set forth in U.S. Patent No. 5,175,315 or copending U.S. Patent Application Serial No. 07/949,107. Removal of the remaining protecting groups thus yields 9ß-hydroxy-desoxo taxol or other 9β-hydroxy-tetracylic taxane having a C13 side chain.

REACTION SCHEME 1

Alternatively, the C13 hydroxy group of 7-protected-9β-hydroxy derivative **6** may be protected with trimethylsilyl or other protecting group which can be selectively removed relative to the C7 hydroxy protecting group as illustrated in Reaction Scheme 2, to enable further selective manipulation of the various substituents of the taxane. For example, reaction of 7,13-protected-9β-hydroxy derivative **7** with KH causes the acetate group to migrate from C10 to C9 and the hydroxy group to migrate from C9 to C10, thereby yielding 10-desacetyl derivative **8**. Protection of the C10 hydroxy group of 10-desacetyl derivative **8** with triethylsilyl yields derivative **9**. Selective removal of the C13 hydroxy protecting group from derivative **9** yields derivative **10** to which a suitable side chain may be attached as described above.
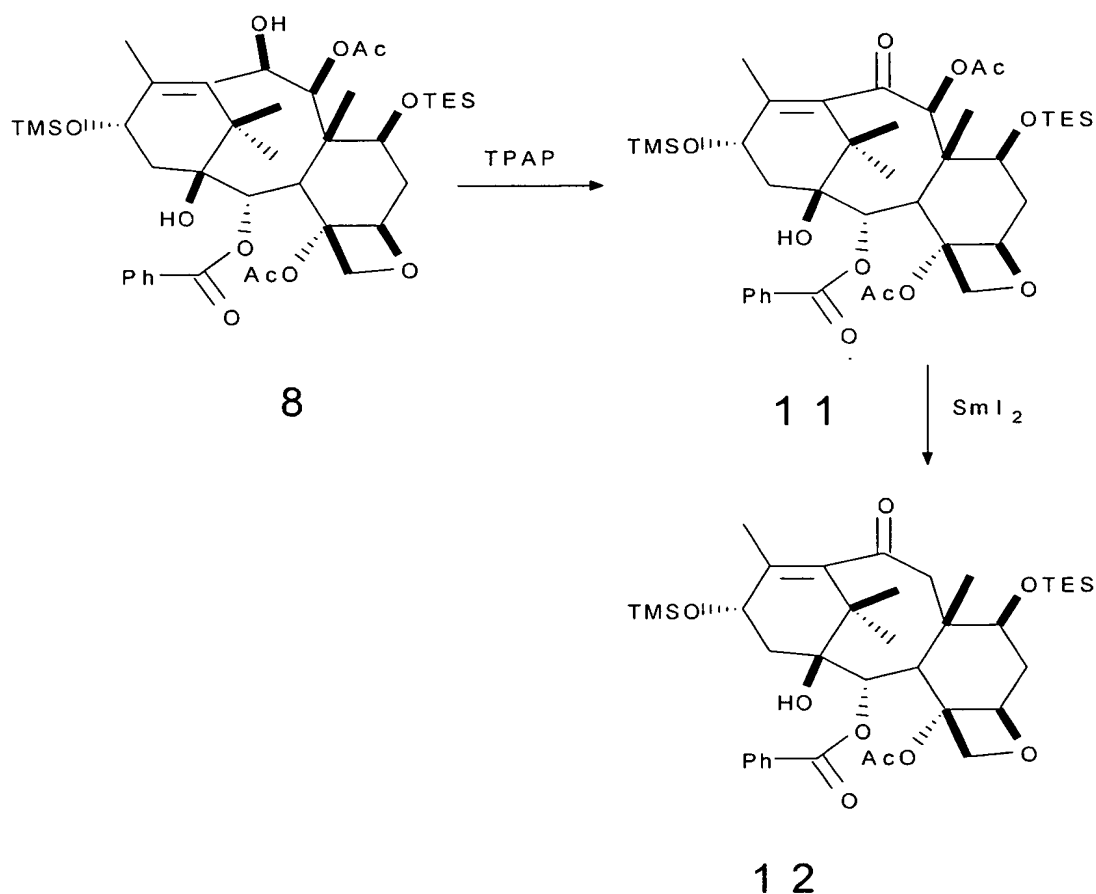
REACTION SCHEME 2

6

1) TMSCl, Et$_3$N

7

2) KH

9

TESCl

ET$_3$N

8

HF

pyridine

10

As shown in Reaction Scheme 3, 10-oxo derivative **11** can be provided by oxidation of 10-desacetyl derivative **8**. Thereafter, the C13 hydroxy protecting group can be

selectively removed followed by attachment of a side chain
as described above to yield 9-acetoxy-10-oxo-taxol or other
9-acetoxy-10-oxotetracylic taxanes having a C13 side chain.
Alternatively, the C9 acetate group can be selectively
removed by reduction of 10-oxo derivative **11** with a
reducing agent such as samarium diiodide to yield 9-desoxo-
10-oxo derivative **12** from which the C13 hydroxy protecting
group can be selectively removed followed by attachment of
a side chain as described above to yield 9-desoxo-10-oxo-
taxol or other 9-desoxo-10-oxotetracylic taxanes having a
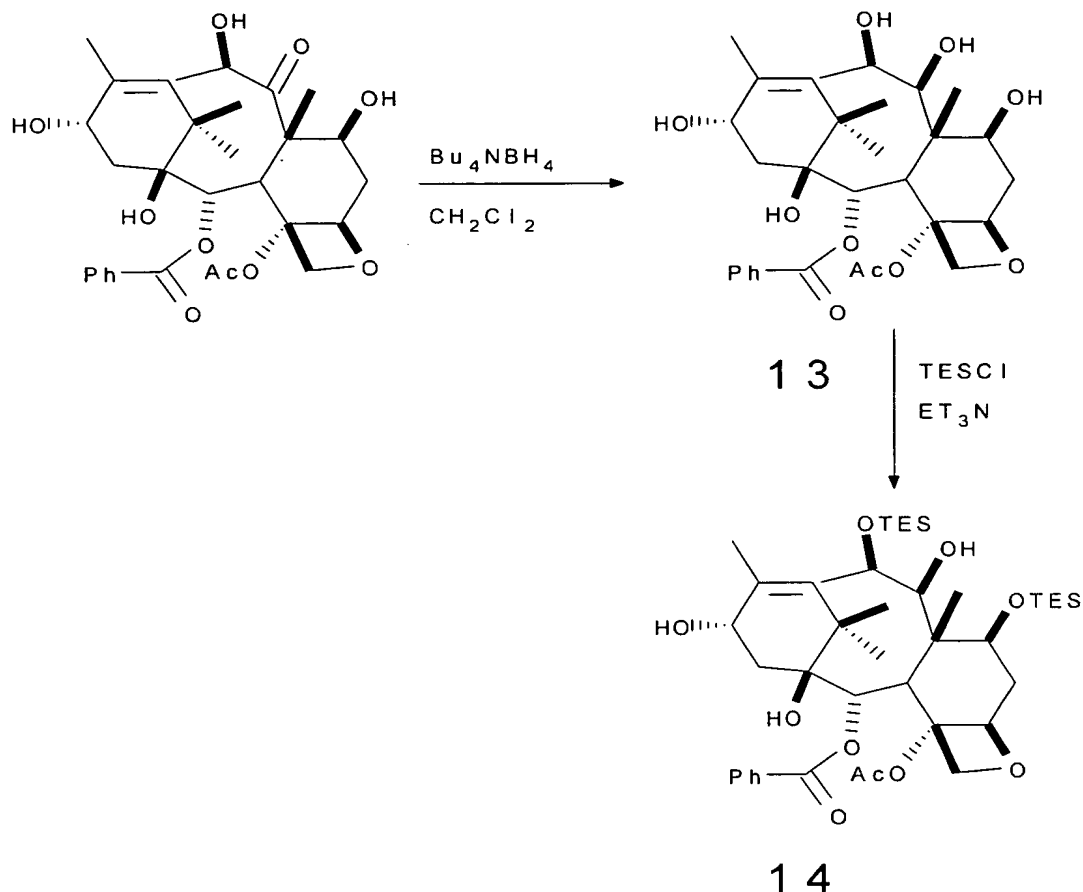C13 side chain.

REACTION SCHEME 3

8   1 1

1 2

Reaction Scheme 4 illustrates a reaction in which 10-
DAB is reduced to yield pentaol **13**. The C7 and C10
hydroxyl groups of pentaol **13** can then be selectively
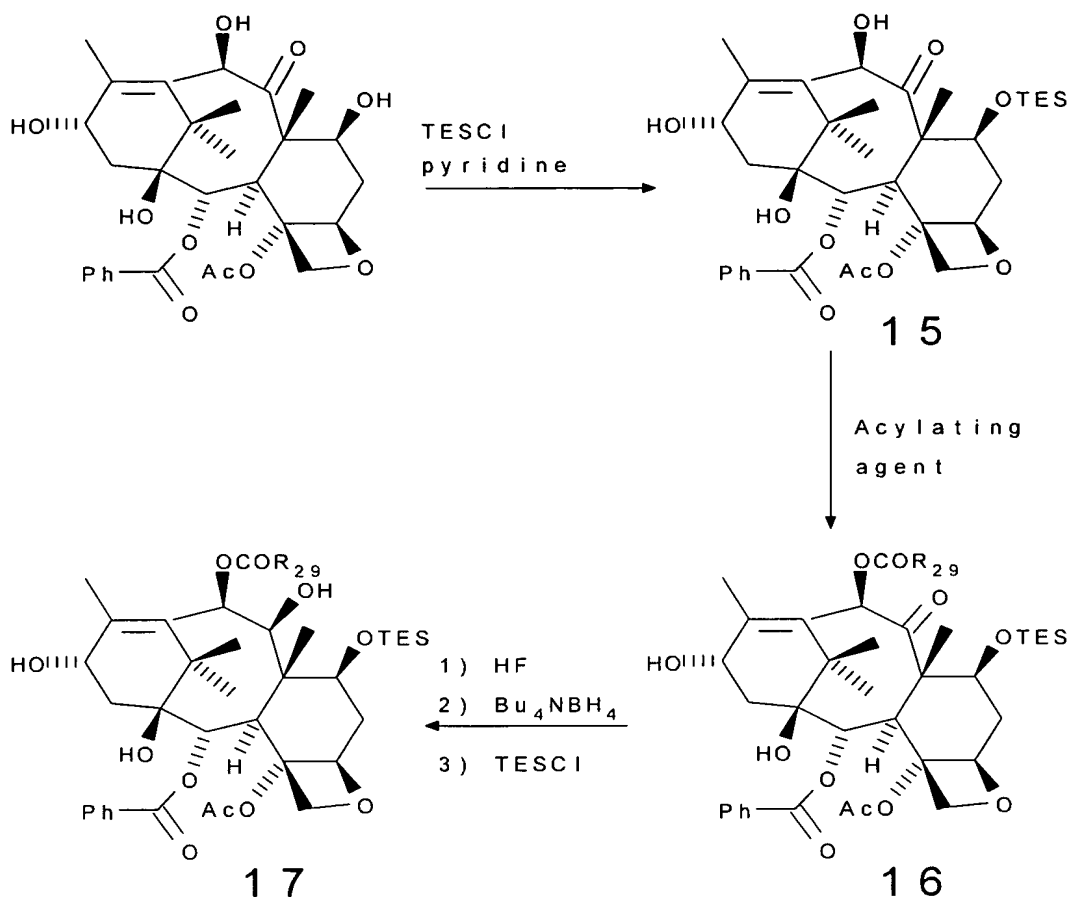protected with the triethylsilyl or another protecting

group to produce triol **14** to which a C13 side chain can be
attached as described above or, alternatively, after
further modification of the tetracylic substituents.

REACTION SCHEME 4

1 3

1 4

Taxanes having C9 and/or C10 acyloxy substituents
other than acetate can be prepared using 10-DAB as a
starting material as illustrated in Reaction Scheme 5.
Reaction of 10-DAB with triethylsilyl chloride in pyridine
yields 7-protected 10-DAB **15**. The C10 hydroxy substituent
of 7-protected 10-DAB **15** may then be readily acylated with
any standard acylating agent to yield derivative **16** having
a new C10 acyloxy substituent. Selective reduction of the
C9 keto substituent of derivative **16** yields 9ß-hydroxy
derivative **17** to which a C13 side chain may be attached.
Alternatively, the C10 and C9 groups can be caused to
migrate as set forth in Reaction Scheme **2**, above.
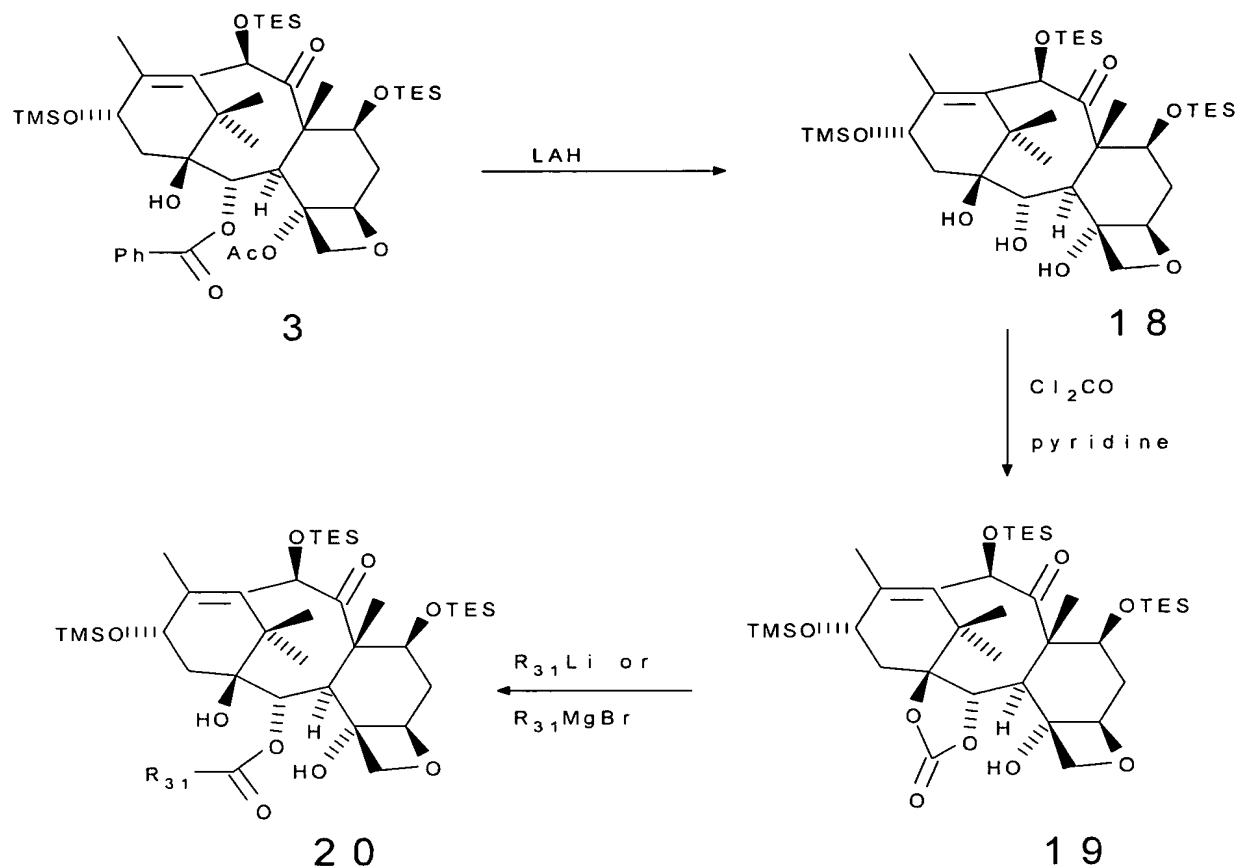
REACTION SCHEME 5

9-desoxo tetracyclic taxanes having alternative C2 and/or C4 esters can be prepared using baccatin III and 10-DAB as starting materials. The C2 and/or C4 esters of baccatin III and 10-DAB can be selectively reduced to the corresponding alcohol(s) using reducing agents such as LAH or Red-Al, and new esters can thereafter be substituted using standard acylating agents such as anhydrides and acid chlorides in combination with an amine such as pyridine, triethylamine, DMAP, or diisopropyl ethyl amine. Alternatively, the C2 and/or C4 alcohols may be converted to new C2 and/or C4 esters through formation of the corresponding alkoxide by treatment of the alcohol with a suitable base such as LDA followed by an acylating agent such as an acid chloride.

Baccatin III and 10-DAB analogs having different substituents at C2 and/or C4 can be prepared as set forth in Reaction Schemes 6-10. To simplify the description, 10-DAB is used as the starting material. It should be understood, however, that baccatin III derivatives or analogs may be produced using the same series of reactions (except for the protection of the C10 hydroxy group) by simply replacing 10-DAB with baccatin III as the starting material. Derivatives of the baccatin III and 10-DAB analogs having different substituents at C9 and at least one other position, for instance C1, C2, C4, C7, C10 and C13, can then be prepared by carrying out any of the other reactions described herein and any others which are within the level of skill in the art.

In Reaction Scheme 6, protected 10-DAB **3** is converted to the triol **18** with lithium aluminum hydride. Triol **18** is then converted to the corresponding C4 ester using Cl_2CO in pyridine followed by a nucleophilic agent (e.g., Grignard reagents or alkyllithium reagents).
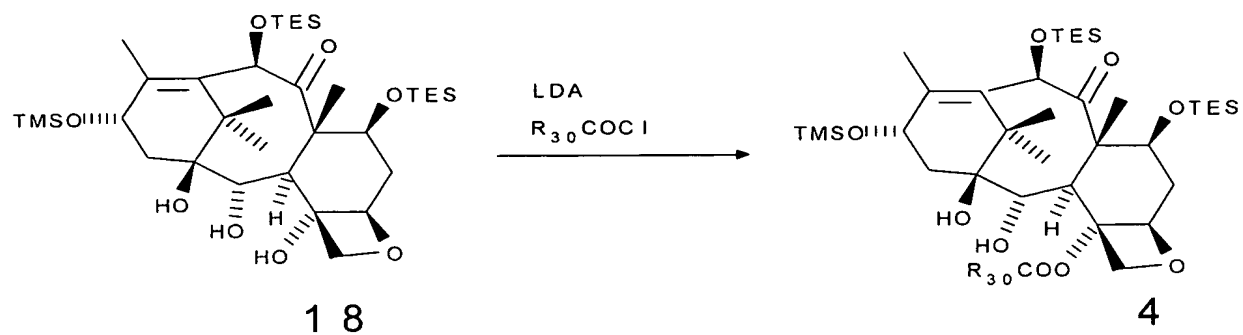
Scheme 6

3

LAH

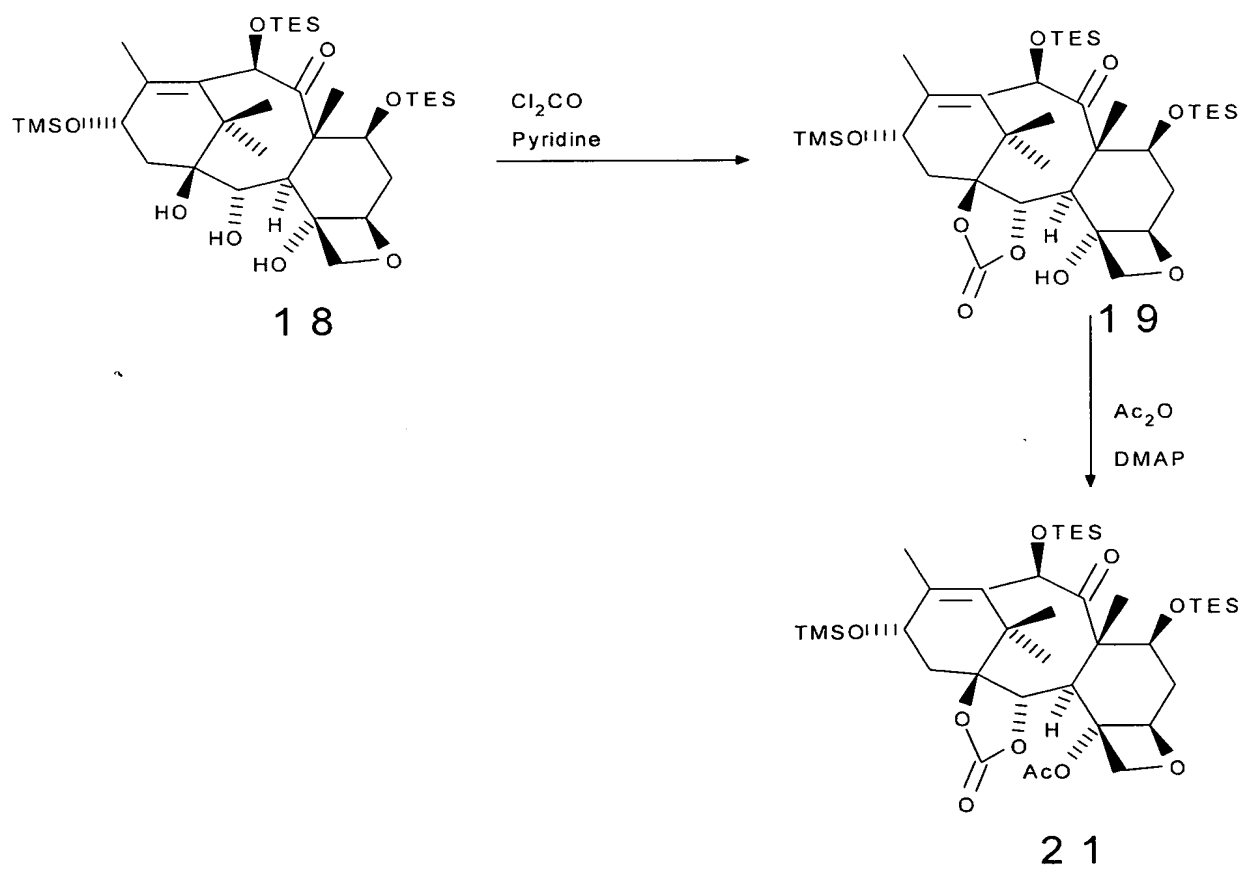18

Cl$_2$CO

pyridine

20

R$_{31}$Li or

R$_{31}$MgBr

19

Deprotonation of triol **18** with LDA followed by
introduction of an acid chloride selectively gives the C4
ester. For example, when acetyl chloride was used, triol
18 was converted to 1,2 diol **4** as set forth in Reaction
Scheme 7.

Triol **18** can also readily be converted to the 1,2
carbonate **19**. Acetylation of carbonate **19** under vigorous
standard conditions provides carbonate **21** as described in
Reaction Scheme 8; addition of alkyllithiums or Grignard
reagents to carbonate **19** provides the C2 ester having a
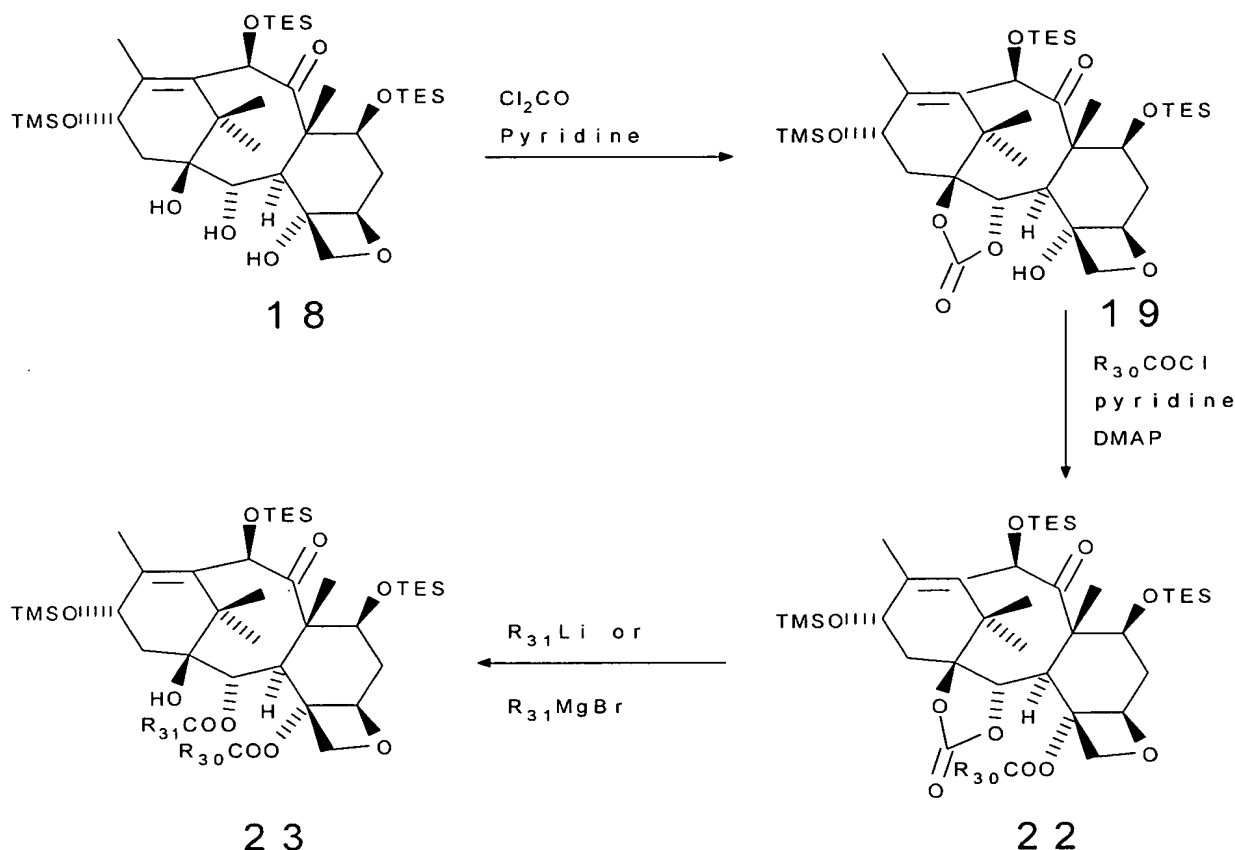free hydroxyl group at C4 as set forth in Reaction Scheme
6.

Scheme 7

Scheme 8

As set forth in Reaction Scheme 9, other C4 substituents can be provided by reacting carbonate **19** with an acid chloride and a tertiary amine to yield carbonate **22** which is then reacted with alkyllithiums or Grignard reagents to provide 10-DAB derivatives having new substituents at C2.
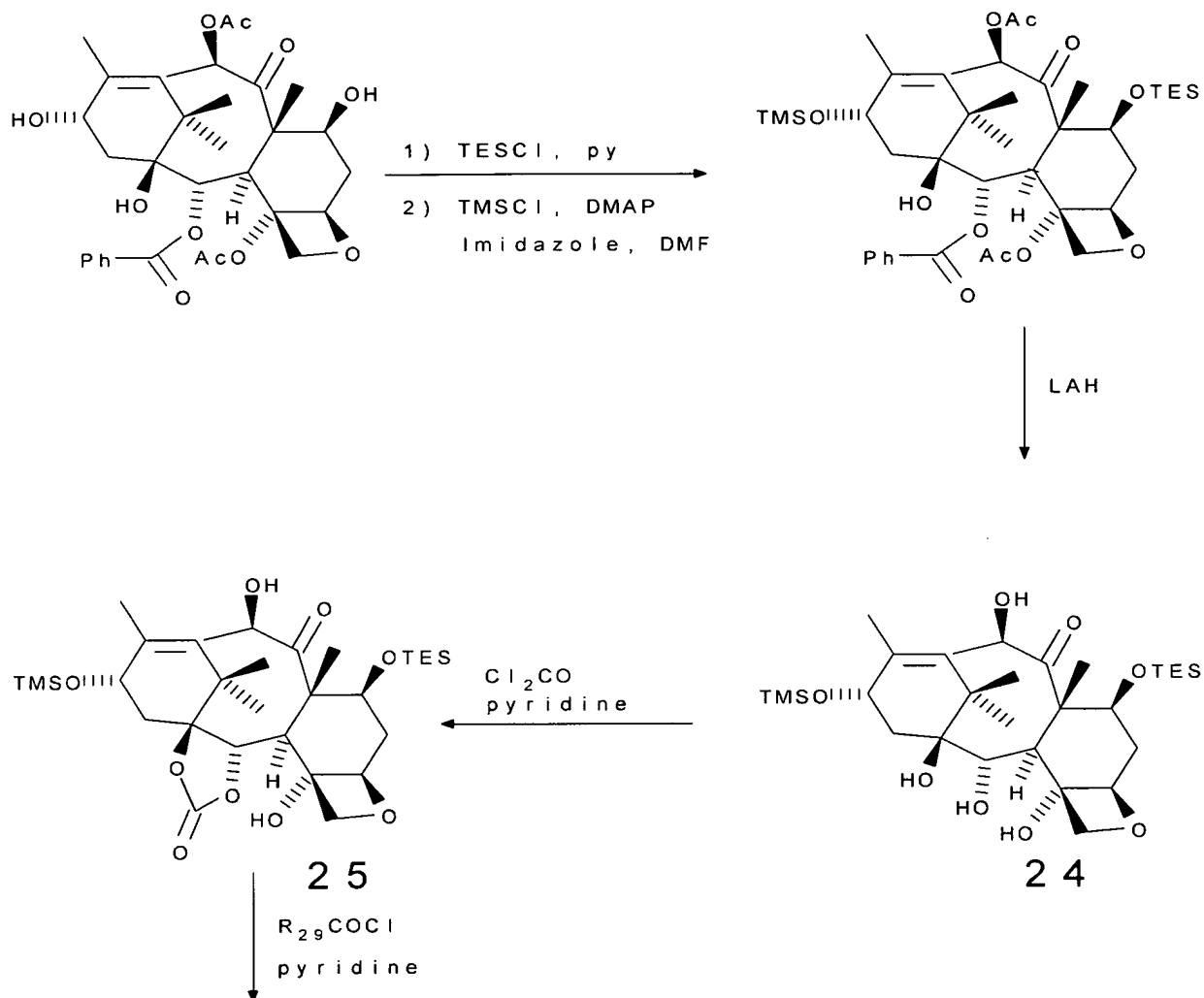
Scheme 9

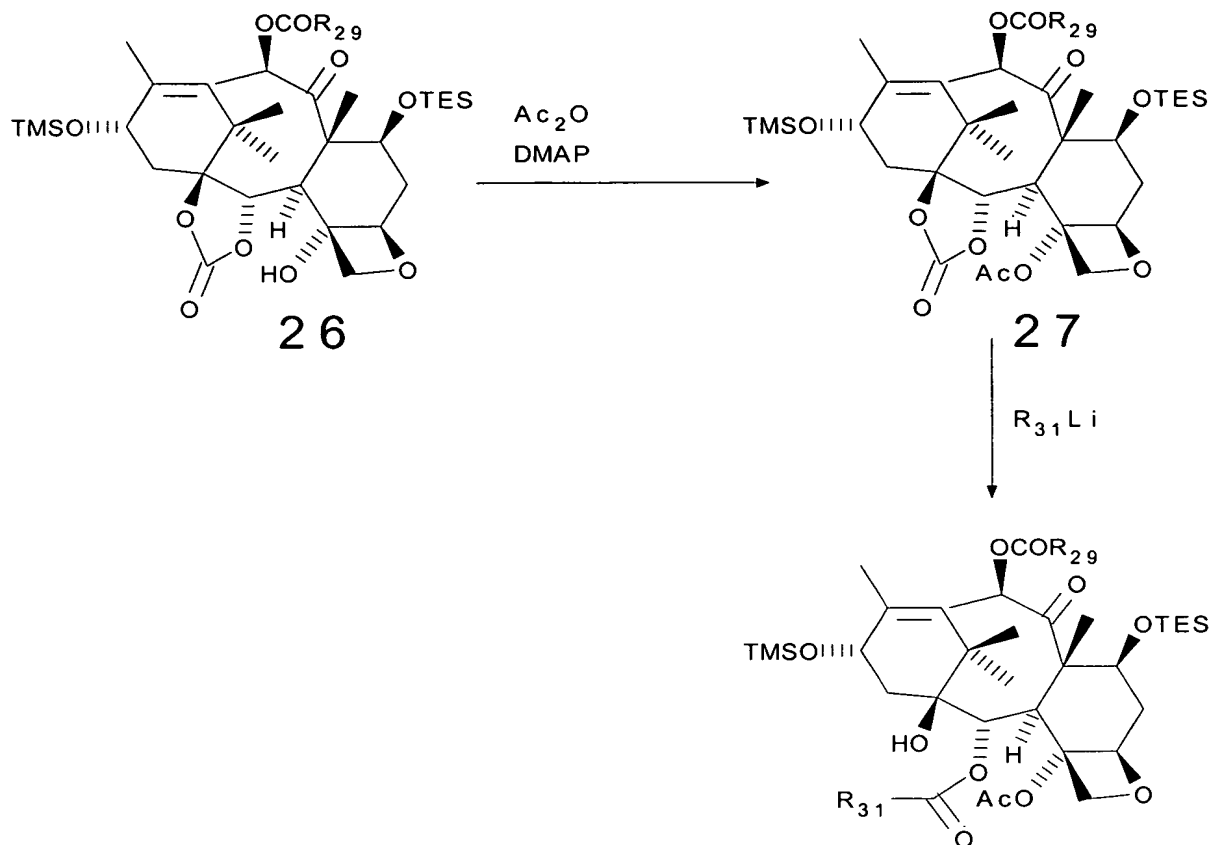Alternatively, baccatin III may be used as a starting material and reacted as shown in Reaction Scheme 10. After being protected at C7 and C13, baccatin III is reduced with LAH to produce 1,2,4,10 tetraol **24**. Tetraol **24** is converted to carbonate **25** using Cl_2CO and pyridine, and carbonate **25** is acylated at C10 with an acid chloride and pyridine to produce carbonate **26** (as shown) or with acetic

anhydride and pyridine (not shown). Acetylation of
carbonate **26** under vigorous standard conditions provides
carbonate **27** which is then reacted with alkyl lithiums to
provide the baccatin III derivatives having new
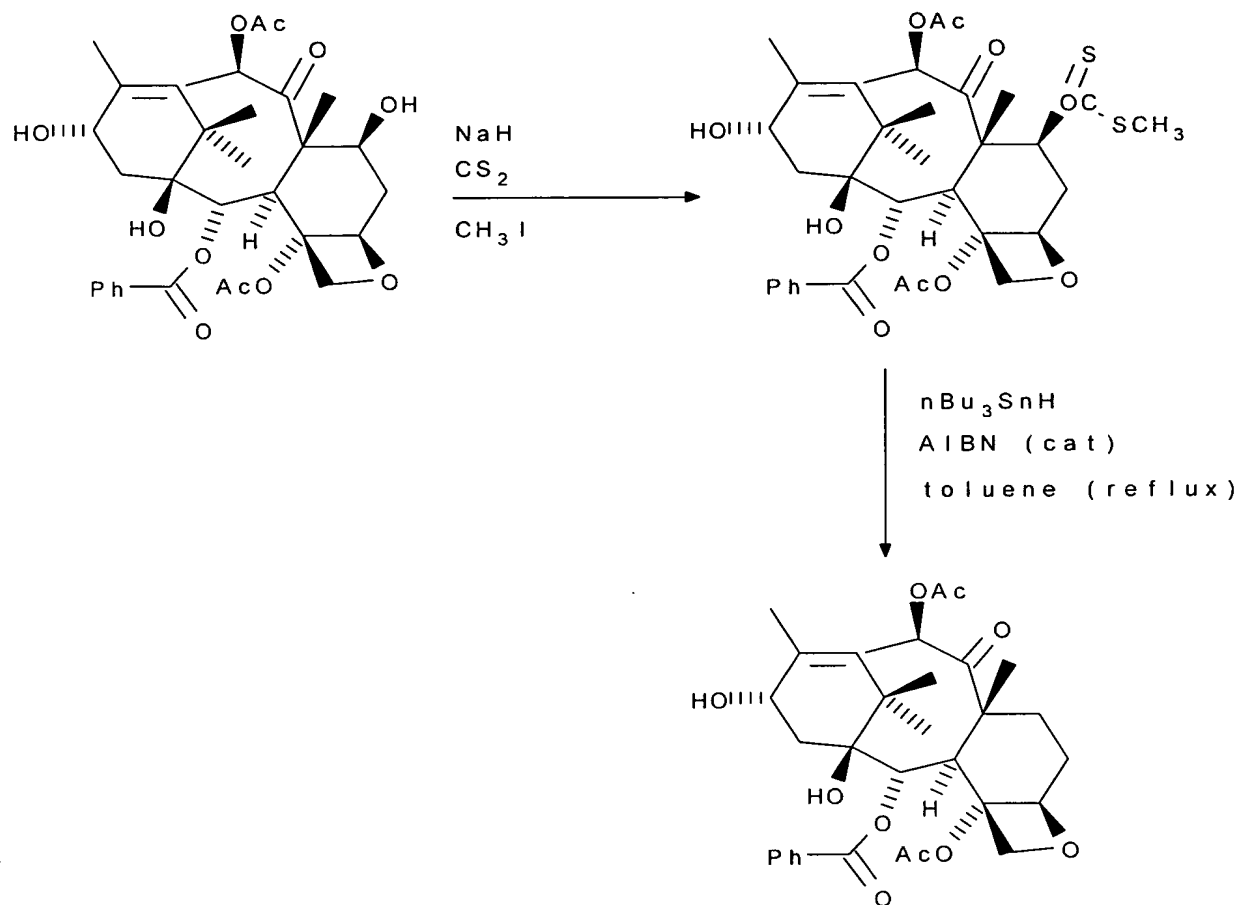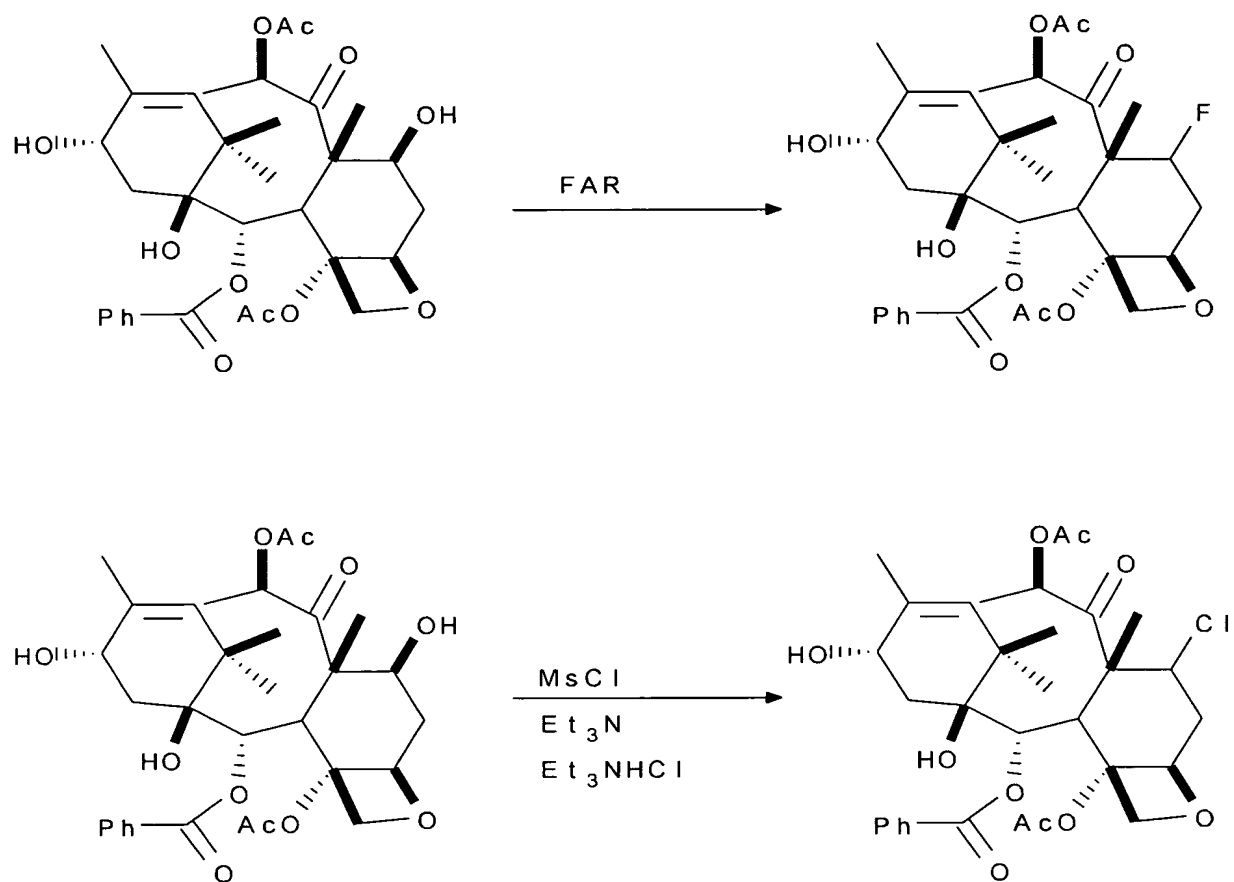substituents at C2 and C10.

<u>Scheme 10</u>

10-desacetoxy derivatives of baccatin III and 10-
desoxy derivatives of 10-DAB may be prepared by reacting
baccatin III or 10-DAB (or their derivatives) with samarium
diiodide. Reaction between the tetracyclic taxane having a
C10 leaving group and samarium diiodide may be carried out
at 0°C in a solvent such as tetra-hydrofuran.
Advantageously, the samarium diiodide selectively abstracts
the C10 leaving group; C13 side chains and other
substituents on the tetracyclic nucleus remain undisturbed.
Thereafter, the C9 keto substituent may be reduced to
provide the corresponding 9-desoxo-9β-hydroxy-10-
desacetyoxy or 10-desoxy derivatives as otherwise described
herein.

C7 dihydro and other C7 substituted taxanes can be
prepared as set forth in Reaction Schemes 11, 12 and 12a.

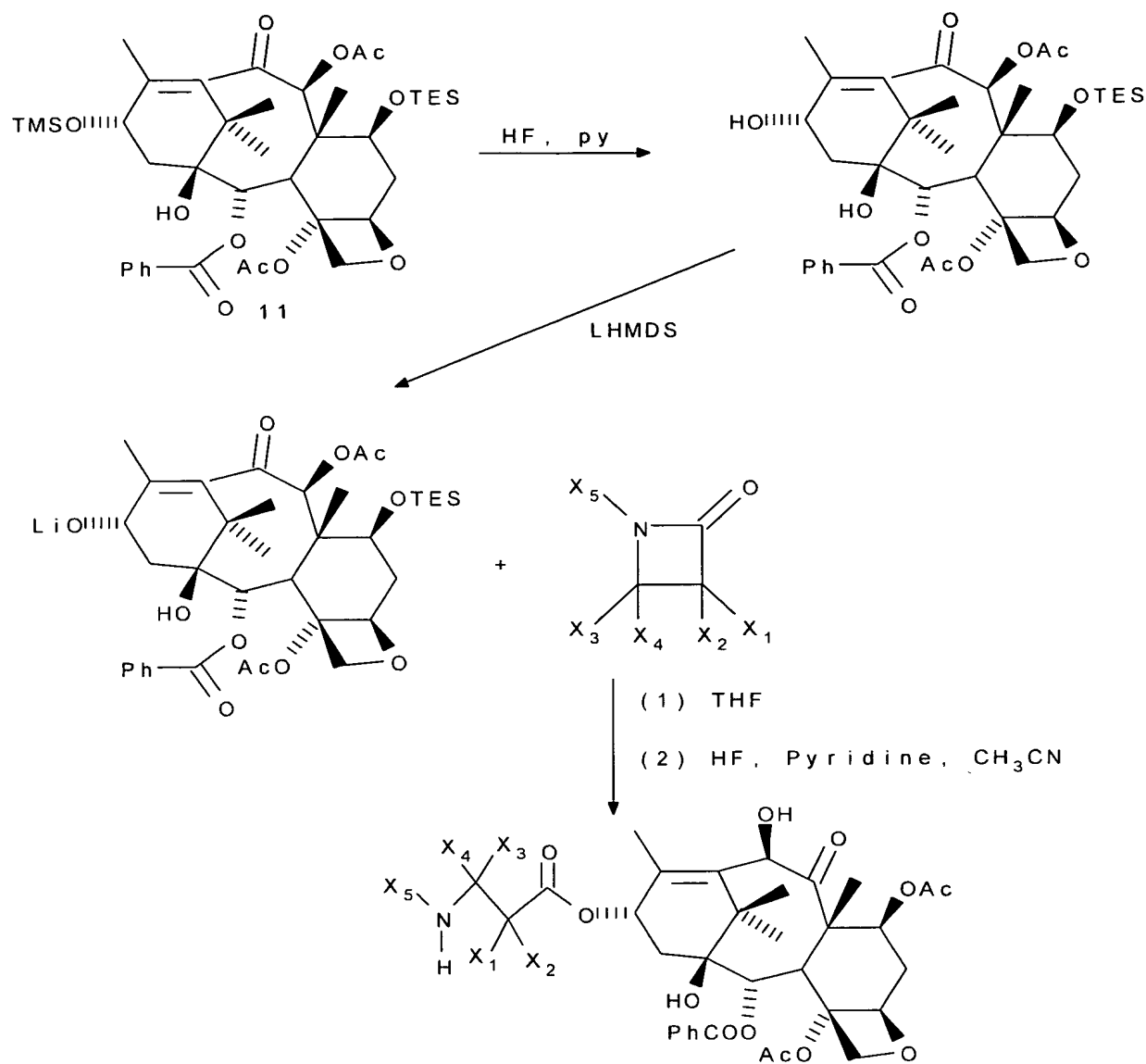REACTION SCHEME 11

REACTION SCHEME 12
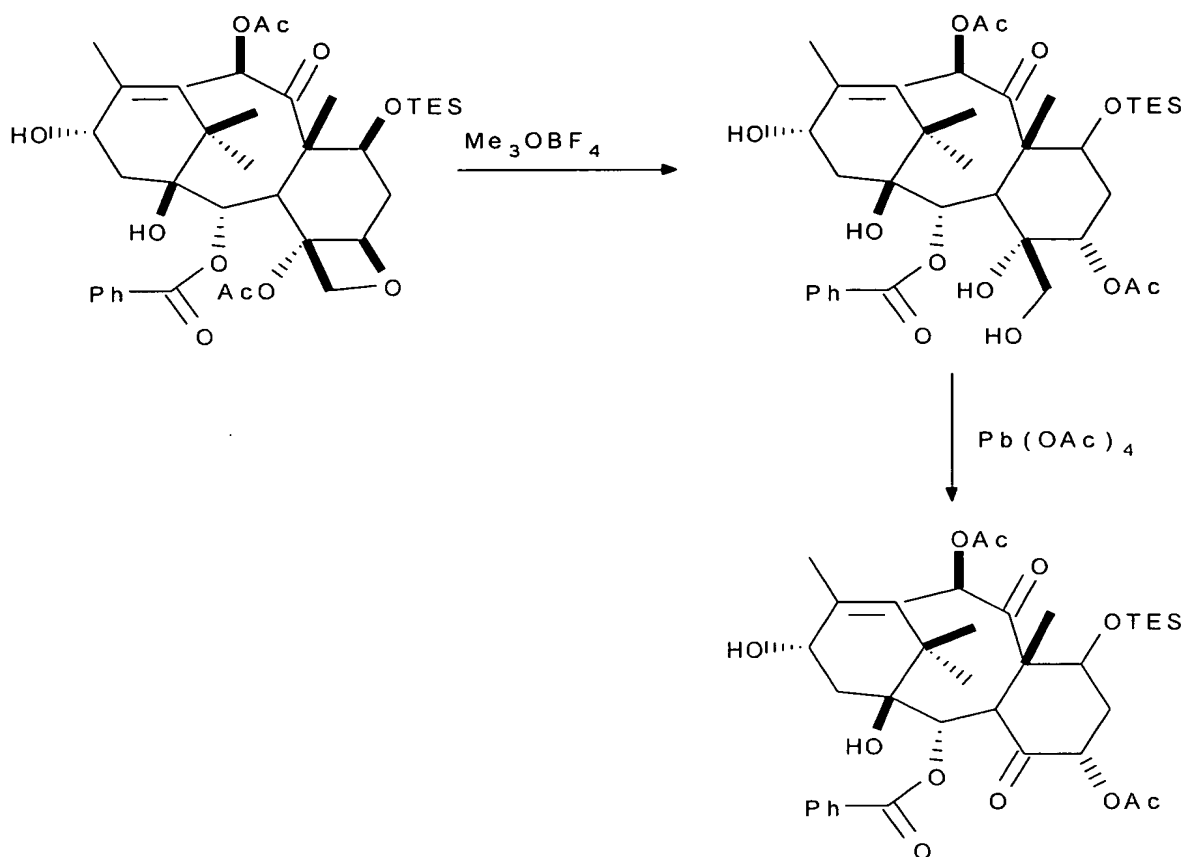
REACTION SCHEME 12a

As shown in Reaction Scheme 12, Baccatin III may be converted into 7-fluoro baccatin III by treatment with FAR at room temperature in THF solution. Other baccatin derivatives with a free C7 hydroxyl group behave similarly. Alternatively, 7-chloro baccatin III can be prepared by treatment of baccatin III with methane sulfonyl chloride

and triethylamine in methylene chloride solution containing
an excess of triethylamine hydro-chloride.

Taxanes having C7 acyloxy substituents can be prepared
as set forth in Reaction Scheme 12a, 7,13-protected 10-oxo-
derivative 11 is converted to its corresponding C13
alkoxide by selectively removing the C13 protecting group
and replacing it with a metal such as lithium. The
alkoxide is then reacted with a β-lactam or other side
chain precursor. Subsequent hydrolysis of the C7
protecting groups causes a migration of the C7 hydroxy
substituent to C10, migration of the C10 oxo substituent to
C9, and migration of the C9 acyloxy substituent to C7.

A wide variety of tricyclic taxanes are naturally
occurring, and through manipulations analogous to those
described herein, an appropriate side chain can be attached
to the C13 oxygen of these substances. Alternatively, as
shown in Reaction Scheme 13, 7-O-triethylsilyl baccatin III
can be converted to a tricyclic taxane through the action
of trimethyloxonium tetrafluoroborate in methylene chloride
solution. The product diol then reacts with lead
tetraacetate to provide the corresponding C4 ketone.

REACTION SCHEME 13

Recently a hydroxylated taxane (14-hydroxy-10-deacetylbaccatin III) has been discovered in an extract of yew needles (C&EN, p 36-37, April 12, 1993). Derivatives of this hydroxylated taxane having the various C2, C4, etc. functional groups described above may also be prepared by using this hydroxylated taxane. In addition, the C14 hydroxy group together with the C1 hydroxy group of 10-DAB can be converted to a 1,2-carbonate as described in C&EN or it may be converted to a variety of esters or other functional groups as otherwise described herein in connection with the C2, C4, C9 and C10 substituents.

The following examples are provided to more fully illustrate the invention.

EXAMPLE 1

10-Deacetyl-9β-hydroxy-9-deoxo baccatin (III).

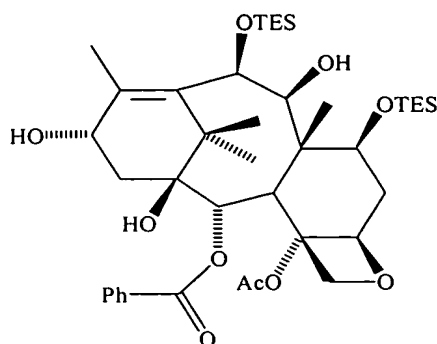A mixture of 10-deacetyl baccatin (III) (300 mg, 0.55 mmol) and n-Bu$_4$NBH$_4$ (709 mg, 2.76 mmol) in 50 mL of CH$_2$Cl$_2$ was stirred for 12 h at room temperature. The resulting mixture was diluted with ethyl acetate, and quenched by stirring with aqueous NaHCO$_3$ solution for 20 min. The organic layer was washed with aqueous NaHCO$_3$ and brine, dried over Na$_2$SO$_4$ and concentrated to give a residue which was purified by flash chromatography. Elution with ethyl acetate- methanol(50:1) afforded 256 mg (85%) of 10-deacetyl-9β-hydroxy-9-deoxo baccatin (III) which was recrystallized from CH$_2$Cl$_2$.

m.p. 209 - 210 ℃; [α]^{25}$_{Na}$ +14.67° (c 0.15, MeOH).

^{1}H NMR (CD$_3$OD, 500 MHz) δ 8.11 (m, 2H, benzoate *ortho*), 7.61 (m, 1H, benzoate, *para*), 7.49 (m, 2H, benzoate, *meta*), 6.11 (d, *J* = 5.5 Hz, 1H, H2), 5.09 (d, *J* = 5.5 Hz, 1H, H10), 4.99 (d, *J* = 8.5 Hz, 1H, H5), 4.80 (ddd, *J* = 10.0, 6.0, 1.5 Hz, 1 H, H13), 4.55 (d, *J* = 5.5 Hz, 1H, H9α), 4.23 (d, *J* = 8.0 Hz, 1H, H20α), 4.13 (dd, *J* = 8.0, 1.0 Hz, 1H, H20β), 3.89 (dd, *J* = 10.0, 7.0 Hz, 1H, H7), 3.23 (d, *J* = 5.5 Hz, 1H, H3), 2.47 (ddd, *J* = 15.0, 8.5, 7.0 Hz, 1H, H6α), 2.33 (dd, *J* = 15.0, 6.0 Hz, 1H, H14α), 2.21 (s, 3H, 4Ac), 2.20 (ddd, *J* = 15.0, 10.0, 1.0 Hz, 1H, H14β), 1.91 (d, *J* = 1.5 Hz, 3H, Me18), 1.83 (ddd, *J* = 15.0, 10.0, 1.0 Hz, 1H, H6β), 1.72 (s, 3H, Me16), 1.59 (s, 3H, Me19), 1.16 (s, 3H, Me17).

EXAMPLE 2

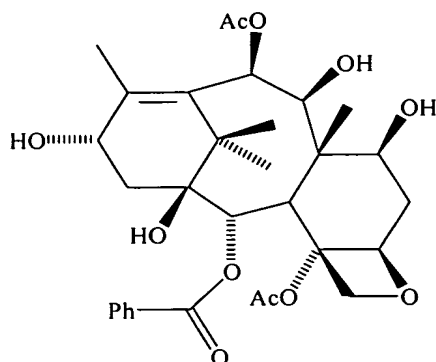## 7,10-bis-O-Triethylsilyl-10-deacetyl-9β-hydroxy-9-deoxo baccatin (III).

To a stirred solution of 10-deacetyl-9β-hydroxy-9-deoxo baccatin (III) (50 mg, 91.6 mmol) and triethylamine (128 mL, 916 mmol) in THF (0.35 mL) was added chlorotriethylsilane (185 mL, 641 mmol), and the reaction mixture was stirred for 24 h at room temperature. The resulting mixture was diluted with ethyl acetate and washed with aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and evaporated to give a residue, which was purified by flash chromato-graphy. Elution with hexane-ethyl acetate (1:1) afforded 53 mg (75%) of 7,10-bis-O-triethylsilyl-10-deacetyl-9β-hydroxy-9-deoxo baccatin (III).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.11 (m, 2H, benzoate *ortho*), 7.57 (m, 1H, benzoate, *para*), 7.47 (m, 2H, benzoate, *meta*), 6.22 (d, *J* = 5.0 Hz, 1H, H2), 5.03 (d, *J* = 5.5 Hz, 1H, H10), 4.88 (d, *J* = 8.7 Hz, 1H, H5), 4.81 (m, 1 H, H13), 4.45 (d, *J* = 5.5 Hz, 1H, H9α), 4.35 (d, *J* = 8.2 Hz, 1H, H20α), 4.22 (d, *J* = 8.2 Hz, 1H, H20β), 3.97 (dd, *J* = 9.2, 7.8 Hz, 1H, H7), 3.15 (d, *J* = 5.0 Hz, 1H, H3), 2.54 (m, 1H, H6α), 2.31 (dd, *J* = 15.5, 10.5 Hz, 1H, H14), 2.29 (s, 3H, 4Ac), 2.01 (dd, *J* = 15.5, 6.4 Hz, 1H, H14), 1.95 (d, *J* = 1.5 Hz, 3H, Me18), 1.94 (m, 1H, H6β), 1.74 (s, 3H, Me16), 1.63 (s, 3H, Me19), 1.16 (s, 3H, Me17) 0.99 (m, 9H, triethylsilyl), 0.67 (m, 6H, triethylsilyl).
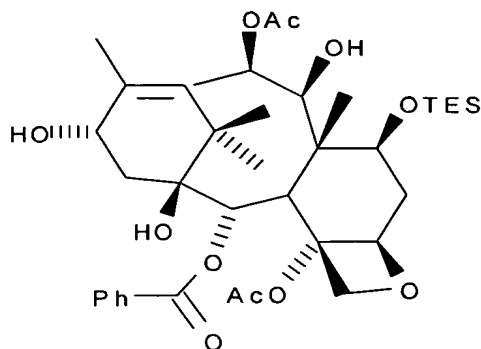
EXAMPLE 3

9β-Hydroxy-9-deoxo baccatin III.

To a solution of baccatin III (215 mg, 0.367 mmol) in 5 mL of CH_2Cl_2 was added n-Bu$_4$NBH$_4$ (944 mg, 3.67 mmol) and the mixture was stirred for 48 h at room temperature. The resulting mixture was diluted with ethyl acetate, and quenched by stirring with aqueous $NaHCO_3$ solution for 20 min. The organic layer was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to give a residue which was separated by flash chromatography. Elution with CH_2Cl_2-acetone (2:1) afforded 111 mg (51%) of 9β-hydroxy-9-deoxo baccatin (III), which was recrystallized from ethyl acetate-ether-hexane.

m.p.160-162 °C; $[\alpha]^{25}_{Na}$ -3.6° (c 0.055 , CHCl$_3$).

^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.11 (m, 1H, benzoate *ortho*), 7.59 (m, 1H, benzoate, *para*), 7.47 (m, 2H, benzoate, *meta*), 6.20 (d, J = 5.0 Hz, 1H, H2β), 6.16 (d, J = 5.5 Hz, 1H, H10), 4.95 (d, J = 6.5 Hz, 1H, H5), 4.82 (dd, J = 8.5, 7.0 Hz, 1 H, H13), 4.44 (d, J = 5.0 Hz, 1H, H9), 4.37 (d, J = 8.0 Hz, 1H, H20α), 4.21 (d, J = 8.0 Hz, 1H, H20β), 4.08 (br t, J = 8.0 Hz, 1H, H7), 3.18 (d, J = 5.0 Hz, 1H, H3), 2.55 (ddd, J = 15.0, 8.0, 7.0 Hz, 1H, H6α), 2.32 (ddd, J = 15.5, 10.0, 1.0 Hz, 1H, H14β), 2.30 (s, 3H, 4Ac), 2.16 (s, 3H, 10Ac), 2.09 (d, J = 1.5 Hz, 3H, Me18), 2.04 (dd, J = 15.5, 6.5 Hz, 1H, H14α), 1.90 (ddd, J = 15.0, 9.0, 2.0 Hz, 1H, H6β), 1.69 (s, 3H, Me16), 1.66 (s, 3H, Me19), 1.11 (s, 3H, Me17).
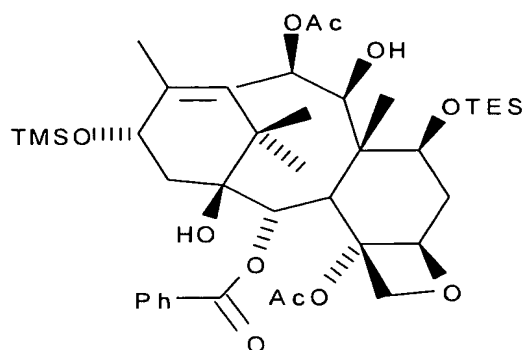
EXAMPLE 4

7-O-Triethylsilyl-9β-hydroxy-9-deoxo baccatin (III).

To a To a solution of triethylamine (0.330 mL, 2.35 mmol) in THF (36 mL) at 0 °C was added triethylsilyl chloride (0.39 mL, 2.35 mmol). To this mixture was added a solution of 9β-hydroxy-9-deoxo baccatin (III) (276 mg, 0.47 mmol) in 10 mL of THF. The solution was warmed to room temperature and stirred for 49 h. MeOH (1 mL) was added and the mixture was stirred for 10 min. The resulting solution was poured into saturated aqueous $NaHCO_3$ (100 mL) and extracted with ethyl acetate (2 x 150 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude residue (0.3 g). Flash column chromatography (CH_2Cl_2-ethyl acetate) afforded 7-O-triethylsilyl-9β-hydroxy-9-deoxo baccatin (III) (297 mg, 89 %).

^{1}H-NMR ($CDCl_3$, 500 Mz), δ 8.11 (dd, J = 1, 7.5 Hz, 2H benzoate ortho), 7.56-7.59 (m, 1H, benzoate), 7.45-7.48 (m, 2H, benzoate), 6.20 (d, J = 5 Hz, 1H, H-2), 6.16 (d, J = 5.5 Hz, 1H, H10), 4.88 (d, J = 9 Hz, 1H, H-5), 4.84 (m, 1H, H-13), 4.63 (br-d, J = 6 Hz, 1H, H-9), 4.36 (d, J = 9 Hz, 1H, H-20α), 4.20 (d, J = 9 Hz, 1H, H-20β), 3.93 (dd, J = 7, 8.5 Hz, 1H, H-7), 3.19 (d, J = 5 Hz, 1H, H-3), 2.63 (br-d, J = 4 Hz, 1H, OH-9), 2.51 (m, 1H, H-6α), 2.47 (d, J = 6 Hz, 1H, OH-10), 2.32 (dd, J = 10, 16 Hz, 1H, H-14β), 2.29 (s, 3H, Ac), 2.21 (d, J = 9 Hz, 1H, OH-13), 2.17 (s, 1H, OH-1), 2.03 (m, 1H, H-14α), 1.98 (d, J = 1.5 Hz, 3H, Me-18), 1.93

(ddd, J = 1.5, 9.5 15 Hz, 1H, H-6β), 1.74 (s, 3H, Me-16),
1.63 (s, 3H, Me-19), 1.17 (s, 3H, Me-17), 0.99 (t, J = 7.5
Hz, 9H, SiCH2CH3), 0.63 and 0.64 (q x 2, J = 7.5 Hz, 6H,
SiCH2CH3).
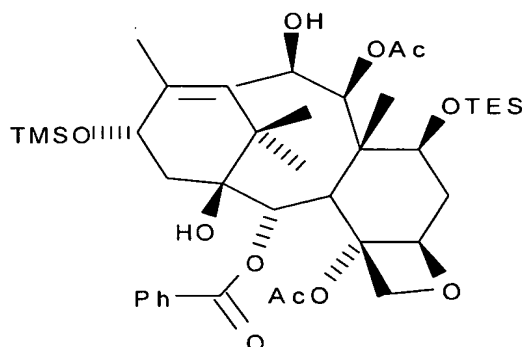
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EXAMPLE 5

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**7-O-Triethylsilyl-9β -hydroxy-9-deoxo-13-O-trimethylsilyl
baccatin (III).**

To a stirred solution of 7-O-triethyl-silyl-9β-
hydroxy-9-deoxo baccatin (III) (140 mg; 0.196 mmol) in
anhydrous pyridine (0.7 mL) at room temperature TMSCl (0.24
mL; 1.9 mmol) was added. After stirring for 36 h the
reaction mixture was diluted with ethyl acetate (50 mL) and
the mixture was poured into saturated aqueous NaHCO₃ (25
mL). The organic phase was washed with saturated aqueous
NaHCO₃ and brine, dried over Na₂SO₄ and evaporated. The
product was isolated by filtration through a small pad of
SiO₂ eluting with 15% EA-hexanes affording 140 mg (94%) of
7-O-triethylsilyl-9β-hydroxy- 9-deoxo-13-O-trimethylsilyl
baccatin (III).
¹H-nmr (300 MHz, CDCl₃) δ 8.10 (dd ; 2H; J=7.7, 1.1 Hz;
o-Bz); 7.58 (t; 1H; J=7.7 Hz; p-Bz); 7.46 (br t; 2H; J=7.7
Hz; m-Bz); 6.12 (d; 1H; J=5.0 Hz; H-2β); 6.10 (d; 1H; J=3.8
Hz; H-10α); 5.00 (br t; 1H; J=8.2 Hz; H-13β); 4.93 (d; 1H;
J=8.8 Hz; H-5α); 4.58 (br d; 1H; J=3.8 Hz; H-9α); 4.33 (d;
1H;J=8.2 Hz; H-20α); 4.14 (d; 1H; J=8.2 Hz; H-20β); 4.01
(dd; 1H; J=8.8, 7.7 Hz; H-7α); 3.12 (d; 1H; J=5.0 Hz;
H-3α); 2.53 (ddd; 1H; J=14.8, 8.8, 7.7 Hz; H-6a); 2.23 (s;

<div align="center">

29

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3H; 4-OAc); 2.21 (br s; 1H; 9-OH); 2.20 (dd; 1H; J=14.0,
8.2 Hz; H-14a); 2.11 (s; 3H; 10-OAc); 2.07 (dd; 1H; J=14.0,
8.2 Hz; H-14β); 2.04 (br s; 3H; 18-Me); 1.89 (brdd; 1H;
J=14.8, 9.9 Hz; H-6β); 1.76 (s; 1H; 1-OH); 1.74 (s; 3H;
16-Me);   1.59 (s, 3H; 19-Me); 1.19 (s, 3H; 17-Me); 0.95
(t; 9H; J=8.0 Hz; 7-TES-Me); 0.65 (m; 6H; TES-CH$_2$); 0.01(s,
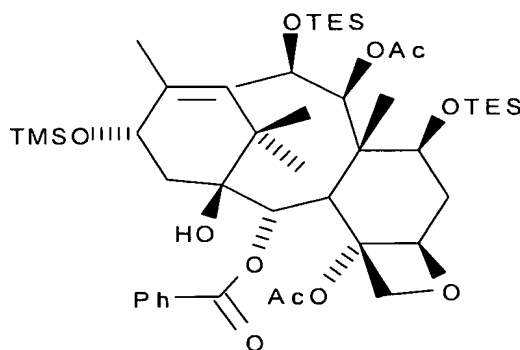9H; TMS).

EXAMPLE 6

7-O-Triethylsilyl-9β-acetoxy-9-deoxo-10-deacetyl-13-O-trimethylsilyl baccatin (III).

To a stirred suspension of KH (250 mg, 35% in mineral
oil, washed 3x1mL with pentane; 2.19 mmol) in anhydrous THF
(2.5 mL) a solution of 7-O-triethyl-silyl-9β-hydroxy-9-
deoxo-13-O-trimethyl-silyl baccatin (III) (142 mg; 0.18
mmol) in anhydrous THF (4 mL) was added at 0°C. After 5 min
the mixture was warmed up to room temperature and stirred
for 30 min and then cooled down to -10°C. The reaction
mixture was quenched with AcOH in THF solution (1.6M; 0.15
mL) and stirred for 5 min at the same temperature before
diluting with ethyl acetate (50 mL). The mixture was
poured into saturated aqueous NaHCO$_3$ (50 mL) and the organic
phase was washed with brine, dried over Na$_2$SO$_4$ and
evaporated. The product was isolated by flash
chromatography (SiO$_2$, 25% ethyl acetate-hexanes) affording
29 mg of recovered starting material (21%) and 107 mg (75%)
of 7-O-tri-ethylsilyl-9β-acetoxy-9-deoxo-10-
deacetyl-13-O-trimethyl-silyl baccatin (III). [1]H-nmr (500

MHz, CDCl$_3$) δ 8.10 (br dd ; 2H; J=7.3, 1.1 Hz; o-Bz); 7.59
(tt; 1H; J=7.3, 1.3 Hz; p-Bz); 7.43 (br t; 2H; J=7.3 Hz;
m-Bz); 6.09 (d; 1H; J=5.9 Hz; H-9α); 6.04 (br d; 1H; J=4.8
Hz; H-2β); 5.25 (dd; 1H; J=5.9, 1.5 Hz; H-10α); 5.05 (br t;
1H; J=8.6 Hz; H-13β); 4.92 (br d; 1H; J=8.8 Hz; H-5α); 4.32
(br d; 1H;J=8.4 Hz; H-20α); 4.09 (dd; 1H; J=8.4, 0.7 Hz;
H-20β); 4.02 (dd; 1H; J=9.2, 7.7 Hz; H-7α); 3.23 (br d; 1H;
J=4.8 Hz; H-3α); 2.56 (ddd; 1H; J=15.0, 9.5, 7.7 Hz; H-6α);
2.26 (s; 3H; 9-OAc); 2.24 (s; 3H; 4-OAc); 2.21 (dd; 1H;
J=15.0, 7.7 Hz; H-14α); 2.16 (d; 1H; J=1.5 Hz; 10-OH); 2.12
(br dd; 1H; J=15.0, 9.7 Hz; H-14β); 1.93 (d; 3H; J=1.1 Hz;
18-Me); 1.89 (brdd; 1H; J=15.0, 9.2, 1.1 Hz; H-6β); 1.715
(s; 3H; 16-Me); 1.71 (s; 1H; 1-OH); 1.42 (s, 3H; 19-Me);
1.28 (s, 3H; 17-Me); 1.02 (t; 9H; J=8.0 Hz; TES-Me); 0.68
(m; 6H; TES-CH$_2$); 0.01 (s, 9H; TMS).

EXAMPLE 7

7,10-bis-O-Triethylsilyl-9β -acetoxy-9-deoxo-10-deacetyl-13-O-trimethylsilyl baccatin (III).

To a solution of 7-O-triethylsilyl-9β-hydroxy-9-
deoxo-13-O-trimethylsilyl baccatin (III) (72 mg; 0.09 mmol)
and triethylamine (128 mL, 916 mmol) in THF (0.35 mL) was
added chlorotriethyl-silane (185 mL, 641 mmol), and the
reaction mixture was stirred for 24 h at room temperature.
The resulting mixture was diluted with ethyl acetate and
washed with aqueous NaHCO$_3$ and brine. The organic layer was
dried over Na$_2$SO$_4$ and concentrated to give a residue, which
was purified by flash chromatography. Elution with hexane-

31

ethyl acetate (1:1) afforded 63 mg (75%) of 7,10-bis-O-triethylsilyl-9β-acetoxy-9-deoxo-10-deacetyl-13-O-tri-methylsilyl baccatin (III).

^{1}H-nmr (500 MHz, CDCl$_3$) δ 8.10 (br dd ; 2H; J=7.3, 1.1 Hz; o-Bz); 7.59 (tt; 1H; J=7.3, 1.3 Hz; p-Bz); 7.43 (br t; 2H; J=7.3 Hz; m-Bz); 6.09 (d; 1H; J=5.9 Hz; H-9α); 6.04 (br d; 1H; J=4.8 Hz; H-2β); 5.10 (d; 1H; J=5.5; H-10α); 5.05 (br t; 1H; J=8.6 Hz; H-13β); 4.92 (br d; 1H; J=8.8 Hz; H-5α); 4.32 (br d; 1H;J=8.4 Hz; H-20α); 4.09 (dd; 1H; J=8.4, 0.7 Hz; H-20β); 4.02 (dd; 1H; J=9.2, 7.7 Hz; H-7α); 3.23 (br d; 1H; J=4.8 Hz; H-3α); 2.56 (ddd; 1H; J=15.0, 9.5, 7.7 Hz; H-6α); 2.26 (s; 3H; 9-OAc); 2.24 (s; 3H; 4-OAc); 2.21 (dd; 1H; J=15.0, 7.7 Hz; H-14α); 2.12 (br dd; 1H; J=15.0, 9.7 Hz; H-14β); 1.93 (d; 3H; J=1.1 Hz; 18-Me); 1.89 (brdd; 1H; J=15.0, 9.2, 1.1 Hz; H-6β); 1.715 (s; 3H; 16-Me); 1.71 (s; 1H; 1-OH); 1.42 (s, 3H; 19-Me); 1.28 (s, 3H; 17-Me); 1.02 (t; 9H; J=8.0 Hz; TES-Me); 0.68 (m; 6H; TES-CH$_2$); 0.01 (s, 9H; TMS).
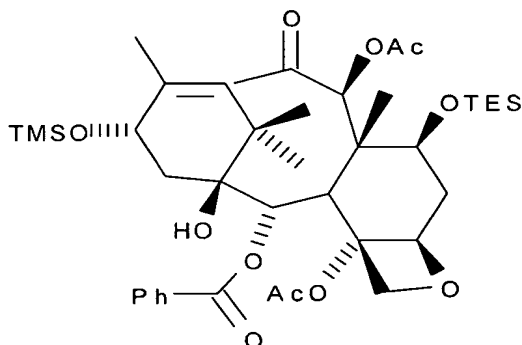
EXAMPLE 8

7-O-Triethylsilyl-9β -acetoxy-9-deoxo-10-deacetoxy-10-oxo-13-O-trimethylsilyl baccatin (III).

A suspension of 7-O-triethylsilyl-9β-acetoxy-9-deoxo-10-deacetyl-13-O- trimethylsilyl baccatin (III) (47 mg; 0.06 mmol), NMO (9 mg; 0.077 mmol) and powdered 4A molecular sieves (25 mg) in anhydrous CH$_2$Cl$_2$ (2.5 mL) was stirred at room temperature for 5 minutes and then a catalytic amount of TPAP was added (1 mg approx.). The

mixture was stirred for 1h and then filtered through a small pad of coarse SiO_2 eluting with 20% ethyl acetate-hexanes. The filtrate was evaporated affording 45.5 mg (97%) of 7-O-Triethyl-silyl-9β-acetoxy-9-deoxo-10-deacetoxy-10-oxo-13-O-tri-methylsilyl baccatin (III).

^{1}H-nmr (500 MHz, $CDCl_3$) δ 8.16 (br dd ; 2H; J=8.2, 1.2 Hz; o-Bz); 7.61 (br tt; 1H; J=7.3, 1.2 Hz; p-Bz); 7.49 (br t; 2H; J=8.0 Hz; m-Bz); 5.84 (d; 1H; J=5.1 Hz; H-2β); 5.26 (2; 1H; H-9α); 5.00 (br s; 1H; w1/2=8 Hz; H-5α); 4.98 (br t; 1H; J=8.2 Hz; H-13β); 4.43 (dd; 1H; J=7.6, 1.0 Hz; H-20β); 4.23 (dd; 1H;J=7.6, 1.0 Hz; H-20α); 4.23 (br overlapped; 1H; H-7α); 3.57 (br d; 1H; J=5.1 Hz; H-3α); 2.32 (dd; 1H; J=14.9, 7.6 Hz; H-14α); 2.31 (s; 3H; 4-OAc); 2.24 (s; 3H; 9-OAc); 2.17 (br dd; 1H; J=14.9, 8.9 Hz; H-14β); 2.07 (d; 3H; J=1.3 Hz; 18-Me); 2.04 (ddd; 1H; J=14.9, 3.6, 2.3 Hz; H-6β); 1.97 (ddd; 1H; J=14.9, 3.3, 2.4 Hz; H-6α); 1.79 (s; 1H; 1-OH); 1.44 (s; 3H; 19-Me); 1.32 (s, 3H; 16-Me); 1.25 (s, 3H; 17-Me); 0.93 (t; 9H; J=8.0 Hz; 7-TES-Me); 0.59 (c; 6H; 7-TES-CH_2); 0.01 (s, 9H; TMS).
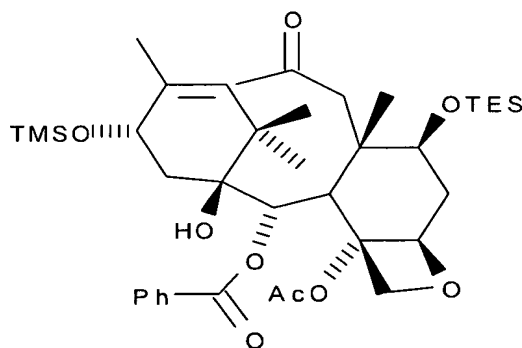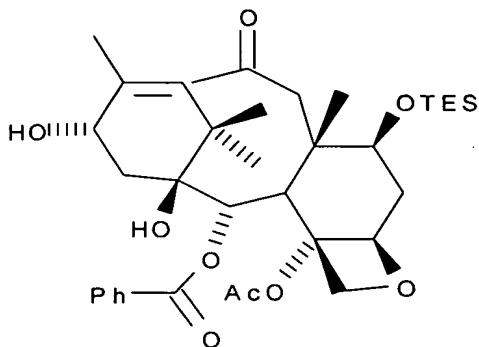
EXAMPLE 9

7-O-Triethylsilyl-9-deoxo-10-deacetoxy-10-oxo-13-O-trimethylsilyl baccatin (III).

To a stirred solution of 7-O-triethylsilyl-9β-acetoxy-9-deoxo-10-deacetoxy-10-oxo- 13-O-trimethylsilyl baccatin (III) (14 mg; 0.018 mmol) in anhydrous THF (0.2 mL) a solution of SmI_2 in THF (0.1M; 1 mL) was added under

nitrogen at room temperature and the resulting solution was
stirred for 1.5 h. The reaction mixture was opened to the
air to quench the excess Sm(II), diluted with ethyl acetate
(20 mL) and the mixture was poured into ice cold 0.2N HCl
and extracted with ethyl acetate; the organic phase was
washed with 5% aqueous citric acid, saturated aqueous NaHCO$_3$
and brine, dried over Na$_2$SO$_4$ and evaporated. The product was
isolated by flash chromatography (SiO$_2$; 15% ethyl
acetate-hexanes) affording 10 mg (81%) of
7-O-triethylsilyl-9-deoxo-10-deacetoxy-10-oxo-13-O-
trimethylsilyl baccatin (III).

^{1}H-nmr (300 MHz, CDCl$_3$) δ 8.13 (br d ; 2H; J=7.5 Hz; o-Bz);
7.62 (br t; 1H; J=7.5 Hz; p-Bz); 7.49 (br t; 2H; J=7.5 Hz;
m-Bz); 5.89 (d; 1H; J=6.0 Hz; H-2β); 4.97 (br t; 1H; J=7.8
Hz; H-13β); 4.91 (d; 1H; J=8.0 Hz; H-5α); 4.33 (br d;
1H;J=8.0 Hz; H-20α); 4.14 (d; 1H; J=8.0 Hz; H-20β); 3.79
(dd; 1H; J=9.0, 6.6 Hz; H-7α); 3.34 (d; 1H; 16.5 Hz; H-9);
3.15 (d; 1H; J=6.0 Hz; H-3α); 2.57 (d; 1H; 16.5 Hz; H-9);
2.49 (ddd; 1H; J=16.5, 9.0, 8.0 Hz; H-6α); 2.25 (s; 3H;
4-OAc); 2.18 (m; 2H; H-14); 1.82 (br s; 3H; 18-Me); 1.75
(ddd; 1H; J=16.5, 6.6, 1.8 Hz; H-6β); 1.72 (s; 1H; 1-OH);
1.48 (s; 3H; Me);   1.38 (s, 3H; Me); 1.23 (s, 3H; Me);
0.99 (t; 9H; J=8.0 Hz; TES-Me); 0.65 (m; 6H; TES-CH$_2$); 0.01
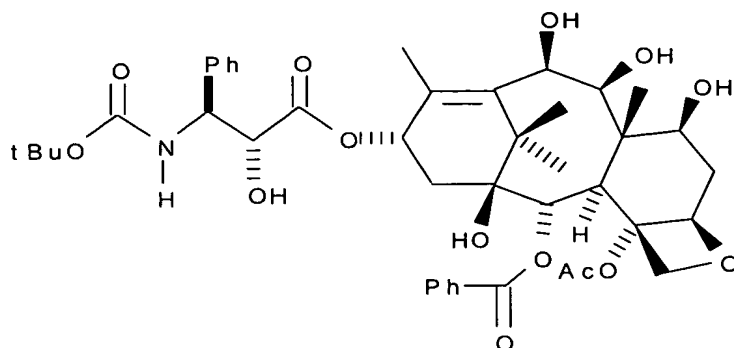(s, 9H; TMS).

EXAMPLE 10

7-O-Triethylsilyl-9-deoxo-10-deacetoxy-10-oxo baccatin (III).

To a solution of 7-O-triethylsilyl-9-deoxo-10-deacetoxy-10-oxo-13-O-trimethylsilyl baccatin (III). (30 mg, .025 mmol) in 2.25 mL of acetonitrile and 2.25 mL of THF in a polyethylene vial was added dropwise .048 mL of pyridine and .075 mL of 48% aqueous HF. The reaction mixture was stirred at room temperature for 12 h and then diluted with ethyl acetate (20 mL). Saturated aqueous sodium bicarbonate was added and the organic layer was separated, washed with brine, dried over anhydrous sodium sulfate and concentrated to give a crude residue. Flash chromatography with 25% ethyl acetate in hexane gave 22 mg (80%) of 7-O-triethylsilyl-9-deoxo-10-deacetoxy-10- oxo baccatin (III).

^{1}H-nmr (300 MHz, CDCl$_3$) δ 8.13 (br d ; 2H; J=7.5 Hz; o-Bz); 7.62 (br t; 1H; J=7.5 Hz; p-Bz); 7.49 (br t; 2H; J=7.5 Hz; m-Bz); 5.89 (d; 1H; J=6.0 Hz; H-2β); 4.97 (br t; 1H; J=7.8 Hz; H-13β); 4.91 (d; 1H; J=8.0 Hz; H-5α); 4.33 (br d; 1H;J=8.0 Hz; H-20α); 4.14 (d; 1H; J=8.0 Hz; H-20β); 3.79 (dd; 1H; J=9.0, 6.6 Hz; H-7α); 3.34 (d; 1H; 16.5 Hz; H-9); 3.15 (d; 1H; J=6.0 Hz; H-3α); 2.57 (d; 1H; 16.5 Hz; H-9); 2.49 (ddd; 1H; J=16.5, 9.0, 8.0 Hz; H-6α); 2.25 (s; 3H; 4-OAc); 2.18 (m; 2H; H-14); 1.82 (br s; 3H; 18-Me); 1.75 (ddd; 1H; J=16.5, 6.6, 1.8 Hz; H-6β); 1.72 (s; 1H; 1-OH); 1.48 (s; 3H; Me); 1.38 (s, 3H; Me); 1.23 (s, 3H; Me); 0.99 (t; 9H; J=8.0 Hz; TES-Me); 0.65 (m; 6H; TES-CH$_2$).

EXAMPLE 11

(67-3)

Preparation of 10-deacetyl-9-desoxo-9β-hydroxy-N-debenzoyl-N-(t-butoxycarbonyl) taxol.

To a solution of 7,10-(bis)triethylsilyl-10-deacetyl-9-desoxo-9β-hydroxy baccatin III (95 mg, 0.123 mmol) in 1 mL of THF at -45 °C was added dropwise 0.250 mL of a 0.98M solution of (TMS)2NLi in THF. After 1 h at -45 °C, a solution of *cis*-1-(t-butoxycarbonyl)-3-triethyl-silyloxy-4-phenylazetidin-2-one (137 mg, 0.37 mmol) in 1 mL of THF was added dropwise to the mixture. The solution was gradually warmed to 0 °C during 6h before 1 mL of aqueous solution was added. The mixture was partitioned between saturated aqueous NaHCO₃ and ethyl acetate. Evaporation of the organic layer gave a residue which was purified by flash chromatography to afford 127 mg of (2'R,3'S)-2',7,10-(tris)triethylsilyl-10-deacetyl-9-desoxo-9β-hydroxy-N-debenzoyl-N-(t-butoxycarbonyl) taxol and 8 mg of the (2'S,3'R) isomer.

To a solution of 90 mg of the major compound obtained from the previous reaction in 1.5 mL of acetonitrile and 2 mL of pyridine at 0 °C was added 0.8 mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3 h, then at 25 °C for 24 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 71 mg of material which was purified by flash chromatography to give 58 mg (92%) of 10-deacetyl-9-desoxo-9β-hydroxy-N-

debenzoyl-N-(t-butoxycarbonyl) taxol, which was
recrystallized from ethyl acetate/ether/hexane.
m.p. 160-161 °C; [α]²⁵Na -18.75 ° (c 0.08 , CHCl₃).
¹H NMR (CD₃OD, 500 MHz) δ 8.10 (d, J = 7.0 Hz, 2H, benzoate
ortho), 7.61 (m, 1H, benzoate, *para*), 7.50 (m, 2H,
benzoate, *meta*), 7.41 (d, J = 8.0 Hz, 2H, phenyl, *ortho*),
7.36 (m, 2H, phenyl, *meta*), 7.28 (m, 1H, phenyl, *para*),6.18
(m, 1H, H13), 6.18 (d, J = 5.5 Hz, 1H, H2β), 5.18 (br s,
1H, H3'), 5.10 (d, J = 5.5 Hz, 1H, H10), 4.99 (d, J = 8.2
Hz, 1H, H5), 4.91 (d, J = 9.3 Hz, 1H, NH), 4.59 (br s, 1H,
H2'), 4.51 (d, J = 5.5 Hz, 1H, H9), 4.22 (d, J = 8.0 Hz, 1H,
H20α), 4.16 (d, J = 8.0 Hz, 1H, H20β), 3.86 (dd, J = 9.5,
7.5 Hz, 1H, H7), 3.13 (d, J = 5.5 Hz, 1H, H3), 2.48 (m, 1H,
H6α), 2.29 (m, 1H, H14α), 2.28 (s, 3H, 4Ac), 2.19 (m , 1H,
H14β), 1.85 (ddd, J = 15.1, 9.6, 1.4 Hz, 1H, H6β), 1.79 (s,
3H, Me16), 1.78 (s, 3H, Me18), 1.61 (s, 3H, Me19H), 1.42
(s, 9H, t-Bu), 1.29 (s, 3H, Me17).

EXAMPLE 12

(70-2)

**Preparation of 3'-desphenyl-3'-(2-thienyl)-N-desbenzoyl-
N-(t-butoxycarbonyl)-9-desoxo-9β—hydroxy-10-desacetyl
taxol.**

    To a solution of 7,10-(bis)-O-triethylsilyl-9-
desoxo-9β-hydroxy-10-deacetyl baccatin (III) (70.0 mg, 0.09
mmol) in 1.0 mL of THF at -45°C was added dropwise 0.10 mL
of a 0.98 M solution of LiN(SiMe₃)₂ in hexane. After 0.5 h
at -45 °C, a solution of *cis*-1-t-butoxy-

carbonyl-3-triethylsilyloxy-4-(2-thienyl)azetidin-2-one
(103.8 mg, 0.27 mmol) in 1.0 mL of THF was added dropwise
to the mixture. The solution was warmed to 0 °C and kept at
that temperature for 1 h before 1 mL of a 10% solution of
AcOH in THF was added.   The mixture was partitioned between
saturated aqueous $NaHCO_3$ and 60/40 ethyl acetate/ hexane.
Evaporation of the organic layer gave a residue which was
purified by filtration through silica gel to give 97.4 mg
of a mixture containing (2'R,3'S)-2',7,10-
(tris)-O-triethylsilyl-3'-desphenyl-3'-(2-thienyl)-N-
desbenzoyl-N-(t-butoxycarbonyl)-9-desoxo-9β-hydroxy-10-
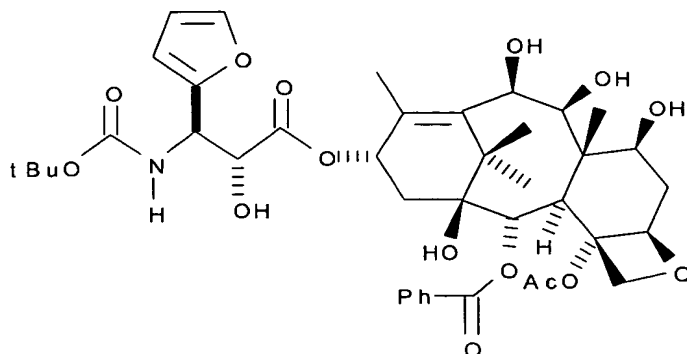desacetyl taxol and a small amount of the (2'S,3'R) isomer.

　　　　To a solution of 97.4 mg (0.084 mmol) of the mixture
obtained from the previous reaction in 13.5 mL of
acetonitrile and 0.57 mL of pyridine at 0 °C was added 1.92
mL of 48% aqueous HF.   The mixture was stirred at 0 °C for 3
h, then at 25 °C for 13 h, and partitioned between saturated
aqueous sodium bicarbonate and ethyl acetate. Evaporation
of the ethyl acetate solution gave 69.4 mg of material
which was purified by flash chromatography to give 63.1 mg
(89%) of 3'-desphenyl-3'-(2-thienyl)-N-desbenzoyl-N-
(t-butoxycarbonyl)-9- desoxo-9β-hydroxy-10-desacetyl taxol,
which was recrystallized from methanol/water.
m.p.146-148°C; $[\alpha]_{Na}^{25}$ -54.2° (c 0.0026, $CHCl_3$).
^{1}H NMR (MeOH, 300 MHz) δ 8.11(d, J=7.1 Hz, 2H, benzoate
ortho), 7.61(m, 1H, benzoate para), 7.48(m, 2H, benzoate
meta), 7.25(dd, J=5.4, 1.2 Hz, 1H, thienyl), 7.14(d, J=3.3
Hz, 1H, thienyl), 7.03(dd, J=5.4, 3.9 Hz, 1H, thienyl),
6.18(m, 1H, H13), 6.18(d, J=5.5 Hz, 1H, H2), 5.23(br s, 1H,
H3'), 5.07(d, J=5.5 Hz, 1H, H10), 4.97(d, J=8.1 Hz, 1H,
H5), 4.84(d, J=9.3 hz, 1H, NH), 4.52(br s, 1H, H2'),
4.50(d, J=5.5 Hz, 1H, H9), 4.23(d, J=8.1, 1H, H20α),
4.16(d, J=8.1 Hz, 1H, H20β), 3.92(dd, J=9.4, 7.5 Hz, 1H,
H7), 3.13(d, J=5.5 Hz, H3), 2.47(m, 1H, H6α), 2.26(m, 1H,
H14α), 2.27(s, 3H, 4Ac), 2.16(m, 1H, H14β), 1.84(ddd,
J=15.1, 9.4, 1.2 Hz, H6β), 1.79(s, 3H, Me16), 1.76(s, 3H,

Me18), 1.62(s, 3H, Me19) 1.39(s, 9H, 3Me t-butoxy), 1.27(s,
3H, Me17).

<div align="center">EXAMPLE 13</div>

(70-3)

**Preparation of 3'-desphenyl-3'-(2-furyl)-N-desbenzoyl-
N-(t-butoxycarbonyl)-9-desoxo-9β-hydroxy-10-desacetyl taxol.**

To a solution of 7,10-(bis)-O-triethylsilyl-9-
desoxo-9β-hydroxy-10-deacetyl baccatin (III) (70.0 mg, 0.09
mmol) in 1.0 mL of THF at -45 °C was added dropwise 0.10 mL
of a 0.98 M solution of LiN(SiMe$_3$)$_2$ in hexane. After 0.5 h
at -45 °C, a solution of cis-1-t-butoxy-carbonyl-3-
triethylsilyloxy-4-(2-furyl)azetidin-2-one (99.5 mg, 0.27
mmol) in 1.0 mL of THF was added dropwise to the mixture.
The solution was warmed to 0 °C and kept at that temperature
for 1 h before 1 mL of a 10% solution of AcOH in THF was
added. The mixture was partitioned between saturated
aqueous NaHCO$_3$ and 60/40 ethyl acetate/ hexane. Evaporation
of the organic layer gave a residue which was purified by
filtration through silica gel to give 94.3 mg of a mixture
containing (2'R,3'S)-2',7,10-(tris)-O-triethylsilyl-3'-
desphenyl-3'-(2-furyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-9-
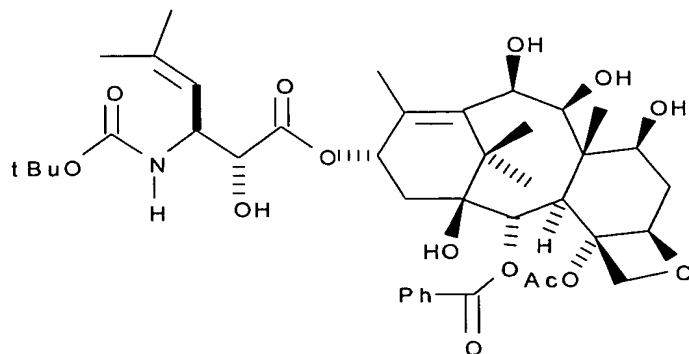desoxo-9β-hydroxy- 10-desacetyl taxol and a small amount of
the (2'S,3'R) isomer.

To a solution of 94.3 mg (0.082 mmol) of the mixture
obtained from the previous reaction in 13.5 mL of
acetonitrile and 0.57 mL of pyridine at 0 °C was added 1.92
mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3

<div align="center">39</div>

h, then at 25 °C for 13 h, and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. Evaporation of the ethyl acetate solution gave 72.3 mg of material which was purified by flash chromatography to give 59.1 mg (89%) of 3'-desphenyl-3'-(2-furyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-9-desoxo- 9β-hydroxy-10-desacetyl taxol, which was recrystallized from methanol/water.
m.p.144-146°C; $[\alpha]_{Na}^{25}$ -54.0° (c 0.0028, CHCl$_3$).
¹H NMR (MeOH, 300 MHz) δ 8.10(d, J=7.1 Hz, 2H, benzoate ortho), 7.60(m, 1H, benzoate para), 7.51(m, 2H, benzoate meta), 7.40(m, 1H, furyl), 6.37(m, 1H, furyl), 6.34(m, 1H, furyl), 6.17(m, 1H, H13), 6.16(d, J=5.4 Hz, 1H, H2), 5.24(br s., 1H, H3'), 5.11(d, J=5.5 Hz, 1H, H10), 4.86(d, J=8.1 Hz, 1H, H5), 4.83(d, J=9.3 hz, 1H, NH), 4.50(d, J=5.5 Hz, 1H, H9), 4.45(br s, 1H, H2'), 4.21(d, J=8.1, 1H, H20α), 4.13(d, J=8.1 Hz, 1H, H20β), 3.92(dd, J=9.4, 7.5 Hz, 1H, H7), 3.11(d, J=5.5 Hz, H3), 2.46(m, 1H, H6α), 2.24(m, 1H, H14α), 2.21(s, 3H, 4Ac), 2.15(m, 1H, H14β), 1.79(ddd, J=15.1, 9.4, 1.2 Hz, H6β), 1.77(s, 3H, Me16), 1.73(s, 3H, Me18), 1.61(s, 3H, Me19), 1.37(s, 9H, 3Me t-buthoxy), 1.26(s, 3H, Me17).

EXAMPLE 14

(70-4)

**Preparation of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-
N-(t-butoxycarbonyl)-9-desoxo-9β-hydroxy-10-desacetyl taxol.**

To a solution of 7,10-(bis)-O-triethylsilyl-9-
desoxo-9β-hydroxy-10-deacetyl baccatin (III) (70.0 mg, 0.09
mmol) in 1.0 mL of THF at -45 °C was added dropwise 0.10 mL
of a 0.98 M solution of $LiN(SiMe_3)_2$ in hexane. After 0.5 h
at -45 °C, a solution of *cis*-1-(t-butoxy-
carbonyl)-3-(2-methoxyisopropyloxy)-4-(isobutenyl)-
azetidin-2-one (84.5 mg, 0.27 mmol) in 1.0 mL of THF was
added dropwise to the mixture. The solution was warmed to 0
°C and kept at that temperature for 1 h before 1 mL of a 10%
solution of AcOH in THF was added. The mixture was
partitioned between saturated aqueous $NaHCO_3$ and 60/40 ethyl
acetate/hexane. Evaporation of the organic layer gave a
residue which was purified by filtration through silica gel
to give 88.3 mg of a mixture containing
(2'R,3'S)-2',7,10-(tris)-O-triethylsilyl-3'-desphenyl-
3'-(isobutenyl)-N-desbenzoyl-N-(t-butoxycarbonyl)-
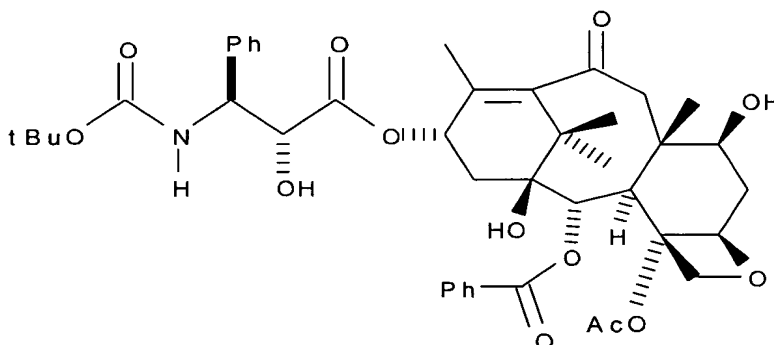9-desoxo-9β-hydroxy-10-desacetyl taxol and a small amount of
the (2'S,3'R) isomer.

To a solution of 88.3 mg (0.080 mmol) of the mixture
obtained from the previous reaction in 13.5 mL of
acetonitrile and 0.55 mL of pyridine at 0 °C was added 1.90
mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3
h, then at 25 °C for 13 h, and partitioned between saturated
aqueous sodium bicarbonate and ethyl acetate. Evaporation

of the ethyl acetate solution gave 67.2 mg of material
which was purified by flash chromatography to give 52.7 mg
(82%) of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-N-
(t-butoxycarbonyl)-9- desoxo-9β-hydroxy-10-desacetyl taxol,
which was recrystallized from methanol/water.
m.p.138-140°C; [α]²⁵$_{Na}$ -55.2° (c 0.0026, CHCl$_3$).

¹H NMR (MeOH, 300 MHz) δ 8.11(d, J=7.1 Hz, 2H, benzoate
ortho), 7.61(m, 1H, benzoate para), 7.48(m, 2H, benzoate
meta),   6.13(m, 1H, H13), 6.12(m, 1H, H2), 5.21(br s., 1H,
H3'), 5.02(d, J=5.3 Hz, 1H, H10), 4.93(d, J=8.1 Hz, 1H,
H5), 4.85(d, J=9.1 hz, 1H, NH), 4.84(d, J=8.5 Hz, 1H,
Me$_2$C=CH-), 4.50(br s, 1H, H2'), 4.50(d, J=5.5 Hz, 1H, H9),
4.22(d, J=8.1, 1H, H20α), 4.18(d, J=8.1 Hz, 1H, H20β),
3.89(dd, J=9.4, 7.5 Hz, 1H, H7), 3.12(d, J=5.5 Hz, H3),
2.45(m, 1H, H6α), 2.31(m, 1H, H14α), 2.29(s, 3H, 4Ac),
2.18(m, 1H, H14β), 1.85(ddd, J=15.1, 9.4, 1.2 Hz, H6β),
1.81(s, 3H, Me16), 1.76(s, 3H, Me18), 1.72(s, 6H, 2Me from
isobuthenyl), 1.61(s, 3H, Me19), 1.39(s, 9H, 3Me
t-buthoxy), 1.26(s, 3H, Me17).

EXAMPLE 15

(74-3)

**Preparation of N-desbenzoyl-N-(t-butoxycarbonyl)-9-
desoxo-10-desacetoxy-10-keto taxol.**

To a solution of 7-O-triethylsilyl-9-desoxo-10-
desacetoxy-10-keto baccatin (III) (30.0 mg, 0.047 mmol) in
0.5 mL of THF at -45 °C was added dropwise 0.05 mL of a 0.98
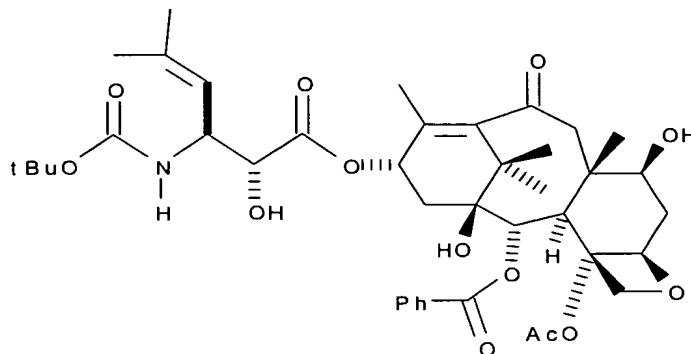M solution of LiN(SiMe$_3$)$_2$ in hexane. After 0.5 h at -45 °C,

a solution of *cis*-1-t-butoxycarbonyl-3-triethyl-
silyloxy-4-phenylazetidin-2-one (53.1 mg, 0.14 mmol) in 0.5
mL of THF was added dropwise to the mixture. The solution
was warmed. to 0 °C and kept at that temperature for 1 h
before 1 mL of a 10% solution of AcOH in THF was added.
The mixture was partitioned between saturated aqueous $NaHCO_3$
and 60/40 ethyl acetate/hexane. Evaporation of the organic
layer gave a residue which was purified by filtration
through silica gel to give 43.7mg of a mixture containing
(2'R,3'S)-2',7-(bis)-O-triethylsilyl-N-
desbenzoyl-N-(t-butoxycarbonyl)-9-desoxo-10-desacetoxy-
10-keto taxol and a small amount of the (2'S,3'R) isomer.

To a solution of 43.7 mg (0.042 mmol) of the mixture
obtained from the previous reaction in 4.0 mL of
acetonitrile and 0.20 mL of pyridine at 0 °C was added 0.50
mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3
h, then at 25 °C for 13 h, and partitioned between saturated
aqueous sodium bicarbonate and ethyl acetate. Evaporation
of the ethyl acetate solution gave 33.2 mg of material
which was purified by flash chromatography to give 24.1 mg
(73%) of N-desbenzoyl-N-(t-butoxycarbonyl)-9-desoxo-10-
desacetoxy-10-keto taxol, which was recrystallized from
methanol/water.

m.p.162-165°C; $[\alpha]_{Na}^{25}$ -58.7° (c 0.0025, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11(d, J=7.1 Hz, 2H, benzoate
ortho), 7.63(m, 1H, benzoate para), 7.50(m, 2H, benzoate
meta), 7.40-7.29(m, 5H, benzoate, phenyl), 6.11(td, J=7.8,
1.0 Hz, 1H, H13), 5.94(d, J=6.4 Hz, 1H, H2), 5.52(d, J=9.8
Hz, 1H, H3'), 5.27(d, J=9.3 Hz, 1H, NH), 4.93(dd, J=8.8 Hz,
1H, H5), 4.64(br s, 1H, H2'), 4.32(d, J=8.3 Hz, 1H, H20α),
4.18(d, J=8.3 Hz, 1H, H20β), 3.88(br s, 1H, 2'OH), 3.71(m,
1H, H7), 3.11(d, J=5.1 Hz, 1H, H3), 3.10(d, J=15.7 Hz, H9α),
2.88(d, J=16.1, 1H, H9β), 2.54(m, 1H, H6α), 2.44(m, 1H,
H14β), 2.29(s, 3H, 4Ac), 2.26(m, 1H, H14α), 2.02(br s, 1H, 7
OH), 1.88(s, 1H, 1 OH), 1.80(m, 1H, H6β), 1.65(s, 3H,
Me18), 1.55(s, 3H, Me16), 1.46(s, 3H, Me19), 1.35(s, 9H,
3Me t-butoxy), 1.29(s, 3H, Me17).(74-4)

EXAMPLE 16

(74-4)

**Preparation of 3'-desphenyl-3'-(isobutenyl)-N-desbenzoyl-
N-(t-butoxycarbonyl)-9-desoxo-10-desacetoxy-10-keto taxol.**

To a solution of 7-O-triethylsilyl-9-desoxo-10-
desacetoxy-10-keto baccatin (III) (30.0 mg, 0.047 mmol) in
0.5 mL of THF at -45 °C was added dropwise 0.05 mL of a 0.98
M solution of LiN(SiMe₃)₂ in hexane. After 0.5 h at -45 °C,
a solution of *cis*-1-t-butoxycarbonyl-3-(2-methoxy-
isopropyloxy)-4-(isobutenyl) azetidin-2-one (44.1 mg, 0.141
mmol) in 0.5 mL of THF was added dropwise to the mixture.
The solution was warmed to 0 °C and kept at that temperature
for 1 h before 1 mL of a 10% solution of AcOH in THF was
added. The mixture was partitioned between saturated
aqueous NaHCO₃ and 60/40 ethyl acetate/hexane. Evaporation
of the organic layer gave a residue which was purified by
filtration through silica gel to give 40.8 mg of a mixture
containing (2'R,3'S)-2'-O-(2-methoxy-isopropyl)-7-O-
triethylsilyl-3'-desphenyl-3'-(iso-butenyl)-N-desbenzoyl-
N-(t-butoxycarbonyl)-9-desoxo-10- desacetoxy-10-keto taxol
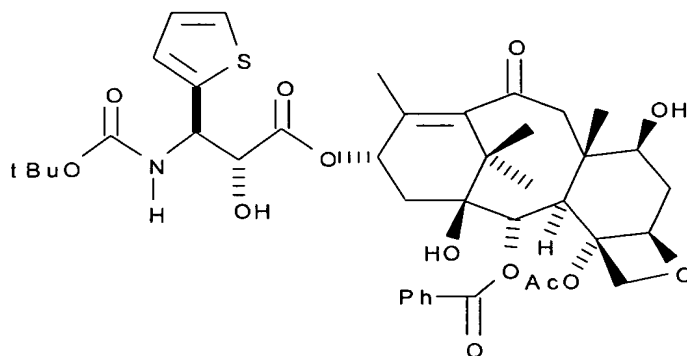and a small amount of the (2'S,3'R) isomer.

To a solution of 40.8 mg (0.043 mmol) of the mixture
obtained from the previous reaction in 4 mL of acetonitrile
and 0.2 mL of pyridine at 0 °C was added 0.5 mL of 48%
aqueous HF. The mixture was stirred at 0 °C for 3 h, then
at 25 °C for 13 h, and partitioned between saturated aqueous
sodium bicarbonate and ethyl acetate. Evaporation of the
ethyl acetate solution gave 34.4 mg of material which was

purified by flash chromatography to give 23.0 mg (70%) of
3'-desphenyl-3'-(isobutenyl)-N- desbenzoyl-N-
(t-butoxycarbonyl)-9-desoxo-10-desacetoxy- 10-keto taxol,
which was recrystallized from methanol/water.
m.p.149-153°C; $[\alpha]^{25}_{Na}$ -56.3° (c 0.0025, CHCl₃).
¹H NMR (CDCl₃, 300 MHz) δ 8.12(d, J=7.2 Hz, 2H, benzoate
ortho), 7.64(m, 1H, benzoate para), 7.51(m, 2H, benzoate
meta), 6.12(t, J=7.5 Hz, 1H, H13), 5.95(d, J=6.2 Hz, 1H,
H2), 5.30(d, J=8.9 Hz, 1H, NH), 4.94(d, J=8.2 Hz, 1H, H5),
4.88(d, J=8.9 Hz, 1H, Me₂C=CH-), 4.79(td, J=8.9, 2.4 Hz, 1H,
H3'), 4.34(d, J=8.2 Hz, 1H, H20α), 4.27(dd, J=5.5, 2.7 Hz,
1H, H2'), 4.19(d, J=8.2 Hz, 1H, H20β),, 3.73(m, 1H, H7),
3.67(br s, 1H, 2'OH), 3.13(d, J=5.1 Hz, 1H, H3), 3.12(d,
J=15.7 Hz, 1H, H9α), 2.90(d, J=15.7 Hz, 1H, H9β), 2.55(m,
1H, H6α), 2.47(m, 1H, H14β), 2.32(s, 3H, 4Ac), 2.28(m, 1H,
H14α), 2.04(br s, 1H, 7 OH), 1.88(s, 1H, 1 OH), 1.82(m,
1H, H6β), 1.79(s, 3H, Me18), 1.76(s, 6H, 2Me from
isobuthenyl), 1.57(s, 3H, Me16), 1.47 (s, 3H, Me19), 1.40(s,
9H, 3Me t-buthoxy) 1.30(s, 3H, Me17).(75-1)

EXAMPLE 17

(75-1)

**Preparation of 3'-desphenyl-3'-(2-thienyl)-N-desbenzoyl-
N-(t-butoxycarbonyl)-9-desoxo-10-desacetoxy-10-keto taxol.**

To a solution of 7-O-triethylsilyl-9-desoxo-10-
desacetoxy-10-keto baccatin (III) (25.0 mg, 0.039 mmol) in
0.5 mL of THF at -45 °C was added dropwise 0.05 mL of a 0.98
M solution of LiN(SiMe₃)₂ in hexane. After 0.5 h at -45 °C,

a solution of *cis*-1-t-butoxycarbonyl-3-triethyl-
silyloxy-4-(2-thienyl)azetidin-2-one (45.0 mg, 0.117 mmol)
in 0.5 mL of THF was added dropwise to the mixture. The
solution was warmed to 0 °C and kept at that temperature for
1 h before 1 mL of a 10% solution of AcOH in THF was added.
The mixture was partitioned between saturated aqueous $NaHCO_3$
and 60/40 ethyl acetate/hexane. Evaporation of the organic
layer gave a residue which was purified by filtration
through silica gel to give 36.2 mg of a mixture containing
(2'R,3'S)-2',7-(bis)-O-triethyl-silyl-3'-desphenyl-3'-
(2-thienyl)-N-desbenzoyl-N-(t- butoxycarbonyl)-9-desoxo-
10-desacetoxy-10-keto taxol and a small amount of the
(2'S,3'R) isomer.

To a solution of 36.2 mg (0.035 mmol) of the mixture
obtained from the previous reaction in 3.0 mL of
acetonitrile and 0.15 mL of pyridine at 0°C was added 0.45
mL of 48% aqueous HF. The mixture was stirred at 0 °C for 3
h, then at 25 °C for 13 h, and partitioned between saturated
aqueous sodium bicarbonate and ethyl acetate. Evaporation
of the ethyl acetate solution gave 29.4 mg of material
which was purified by flash chromatography to give 24.3 mg
(87%) of 3'-desphenyl-3'-(2-thienyl)-N- desbenzoyl-N-
(t-butoxycarbonyl)-9-desoxo-10-desacetoxy-10-keto taxol,
which was recrystallized from methanol/water.
m.p.163-169°C; $[\alpha]_{Na}^{25}$ -54.2° (c 0.0023, $CHCl_3$).
¹H NMR ($CDCl_3$, 300 MHz) δ 8.12(d, J=7.3 Hz, 2H, benzoate
ortho), 7.64(m, 1H, benzoate para), 7.51(m, 2H, benzoate
meta), 7.26(m, 1H, thienyl), 7.10(d, J=3.4 Hz, 1H,
thienyl), 6.99(dd, J=5.1, 3.4 Hz, 1H, thienyl), 6.12(td,
J=6.1, 1.0 Hz, 1H, H13), 5.95(d, J=5.9 Hz, 1H, H2), 5.50(d,
J=4.4 Hz, 1H, NH), 5.42(d, J=9.8 Hz, 1H, H3'), 4.94(d,
J=8.3 Hz, 1H, H5), 4.64(dd, J=4.2, 2.0 Hz, 1H, 2'),
4.33(d, J=7.8 Hz, 1H, H20α), 4.18(d, J=7.8 Hz, 1H, H20β),
3.90(br s, 1H, 2'OH), 3.73(m, 1H, H7), 3.11(d, J=15.8 Hz,
H9α), 3.09(d, J=5.1 Hz, 1H, H3), 2.90(d, J=15.6 Hz, 1H,
H9β), 2.54(m, 1H, H6α), 2.45(m, 1H, H14β), 2.31(s, 3H, 4Ac),
2.28(m, 1H, H14α),, 2.01(br s, 1H, 7 OH), 1.88(s, 1H, 1 OH),

1.83(m, 1H, H6β), 1.69(s, 3H, Me18), 1.56(s, 3H, Me16),
1.46(s, 3H, Me19), 1.40(s, 9H, 3Me t-buthoxy), 1.29(s, 3H,
Me17).

EXAMPLE 18

Taxanes 67-3, 70-2, 70-3, 70-4, 75-1, 74-4, and 74-3 of
Examples 11-17 were evaluated in in vitro cytotoxicity
activity against human colon carcinoma cells HCT-116.
Cytotoxicity was assessed in HCT116 human colon carcinoma
cells by XTT (2,3-bis(2-methoxy-4-nitro-5-
sulfophenyl)-5-[(phenyl-amino)carbonyl]-2H-tetrazolium
hydroxide) assay (Scudiero et al, "Evaluation of a soluble
tetrazolium/ formazan assay for cell growth and drug
sensitivity in culture using human and other tumor cell
lines", Cancer Res. 48:4827-4833, 1988). Cells were plated
at 4000 cells/well in 96 well microtiter plates and 24
hours later drugs were added and serial diluted. The cells
were incubated at 37ºC for 72 hours at which time the
tetrazolium dye, XTT, was added. A dehydro-genase enzyme
in live cells reduces the XTT to a form that absorbs light
at 450 nm which can be quantitated spectrophotometrically.
The greater the absorbance the greater the number of live
cells. The results are expressed as an IC_{50} which is the
drug concentration required to inhibit cell proliferation
(i.e. absorbance at 450 nm) to 50% of that of untreated
control cells.

All compounds had an IC_{50} less than 0.1, indicating
that they are all cytotoxically active.